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Journal of the International Anesthesia Research Society

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The Logical Choice

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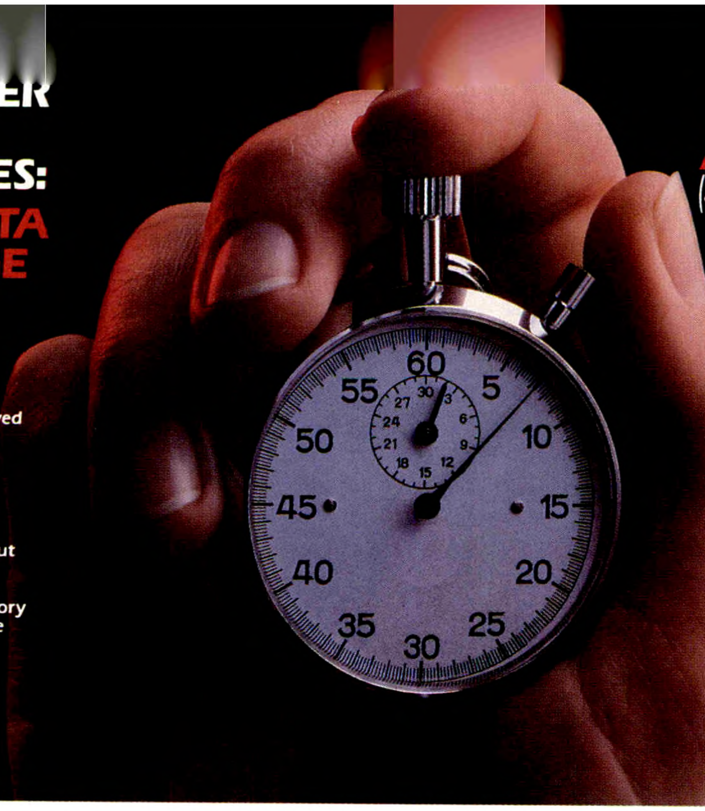
FOR SHORTER SURGICAL PROCEDURES: THE ALFENTA ADVANTAGE

*As with all potent opioids, appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained. The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery.



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Postoperative respiratory depression is of short duration*

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription

DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 µg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.

CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS. AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE. BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY. ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 µg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 µg/kg). The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.

General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery. Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance. Administration of ALFENTA infusion should be discontinued at leas 10-15 minutes prior to the end of surgery. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.

Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.

Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.

ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N=785)	Fentanyl (N=243)	Thiopental Sodium (N=66)	Enflurane (N=55)	Halothane (N=18)	Saline Placebo* (N=18)
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

Manufactured by Taylor Pharmacal Co. for

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Piscataway, N.J. 08854

March 1987, April 1988
U.S. Patent No. 4,167,574
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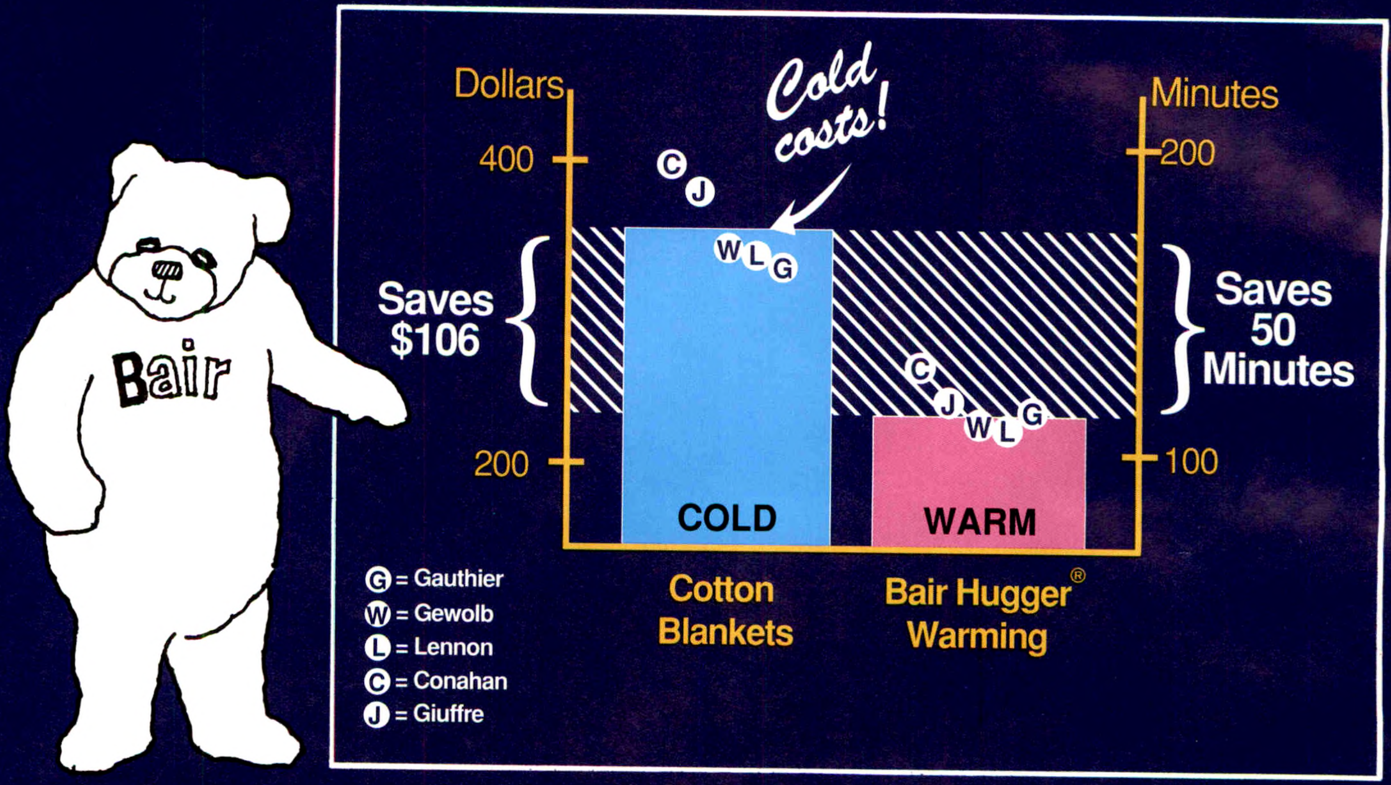

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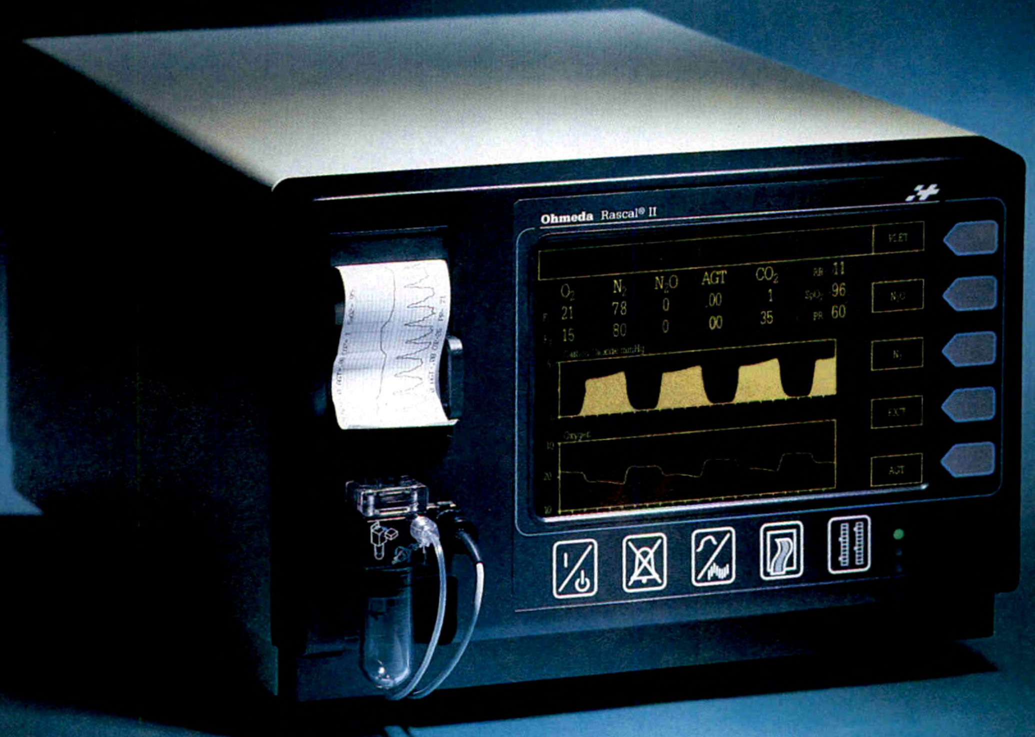

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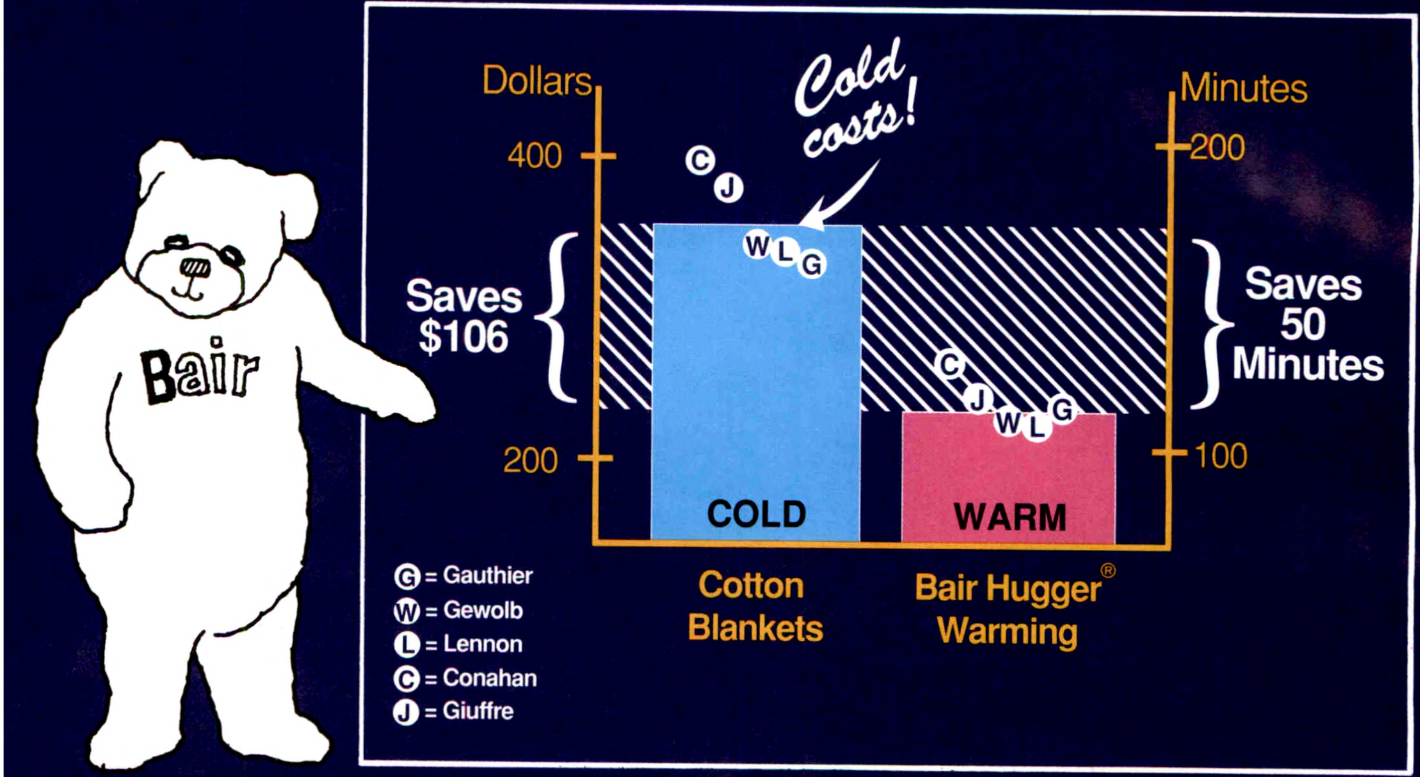

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PRECAUTIONS: General: Since ARDUAN® has little or no effect on the heart rate, the drug will not counteract the bradycardia produced by many opioid anesthetic agents or vagal stimulation. Consequently, bradycardia during anesthesia may be more common with ARDUAN® than when a muscle relaxant (such as pancuronium) which exerts vagolytic action is employed.

Renal Failure: ARDUAN®, in the dose of 70 µg/kg actual body weight (ABW), has been studied in a limited number of patients (n=20) undergoing renal transplant surgery recently dialyzed in preparation for cadaver renal transplant. The mean clinical duration (injection to 25% recovery) of 103 minutes was not judged prolonged; however, there was wide individual variation (30 to 267 minutes). ARDUAN® has not otherwise been studied in patients with renal failure (for elective or emergency non-renal surgery). Because it is primarily excreted by the kidney, and because some shorter-acting drugs (vecuronium and atracurium) have a more predictable duration of action in patients with renal dysfunction, ARDUAN® should be used with extra caution in patients with renal failure.

Increased Volume of Distribution: Conditions associated with an increased volume of distribution, eg, slower circulation time in cardiovascular disease, old age, or edematous states, may be associated with a delay in onset time. Because higher doses of ARDUAN® may produce a longer duration of action, the initial dose should not usually be increased in these patients to enhance onset time; instead, more time should be allowed for the drug to achieve maximum effect.

Hepatic Disease: There are no data on dosage requirements, onset, duration, or pharmacokinetics in patients with moderate or severe hepatic dysfunction and/or biliary obstruction. This should be considered in selection of muscle relaxants for use in these patients.

Obesity: The most common patient condition associated with prolonged clinical duration was obesity, defined as 30% or more over ideal body weight (IBW). Clinical study subjects were dosed on the basis of actual body weight, which may have contributed to the higher incidence of prolonged duration. It is therefore recommended that dosage be based upon ideal body weight for height in obese patients.

Malignant Hyperthermia (MH): Human malignant hyperthermia has not been reported with the administration of ARDUAN®. Because ARDUAN® is never used alone and because the occurrence of malignant hyperthermia during anesthesia is possible even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis, and treatment of malignant hyperthermia prior to the start of any anesthetic. In an animal study in MH-susceptible swine (n=7), the administration of ARDUAN® was not associated with the development of malignant hyperthermia.

Central Nervous System: ARDUAN® has no known effect on consciousness, the pain threshold, or cerebration. Therefore, administration must be accompanied by adequate anesthesia.

Drug Interactions: ARDUAN® can be administered following recovery from succinylcholine when the latter is used to facilitate endotracheal intubation.

The use of ARDUAN® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, is not recommended because it has not been studied.

There are no clinical data on concomitant use of ARDUAN® and other non-depolarizing neuromuscular blocking agents.

Inhalational Anesthetics: Use of volatile inhalation anesthetics has been shown to enhance the activity of other neuromuscular blocking agents on the order of enflurane > isoflurane > halothane. No definite interaction between ARDUAN® and halothane, as used clinically, has been demonstrated. Use of isoflurane in one study of 25 patients resulted in an increase in mean clinical duration by 12%. In another study of 25 patients first anesthetized with enflurane for 5 minutes or more, the mean clinical duration was increased by 50%. Therefore, a prolonged clinical duration following initial or maintenance doses and prolonged recovery from neuromuscular blocking effect of ARDUAN® should generally be anticipated with enflurane > isoflurane > halothane.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for ARDUAN®. ARDUAN®-induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). In addition, experience with other drugs has suggested that acute (eg, diarrhea) or chronic (eg, adrenocortical insufficiency) electrolyte imbalance may alter neuromuscular blockade. Since electrolyte imbalance and acid-base imbalance are usually mixed, either enhancement or inhibition may occur. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies in animals have not been performed to evaluate carcinogenic potential or impairment of fertility. Mutagenicity studies (Ames test, Sister Chromatid Exchange) conducted with ARDUAN® revealed no mutagenic potential.

Pregnancy Category C: A teratogenicity study has been conducted in rats using intravenously administered doses of ARDUAN® approximating the clinical dose in humans (50 µg/kg). No teratogenic effects were observed in this study. An embryotoxic effect (secondary to maternal toxicity) was observed at the highest dose administered (50 µg/kg) as demonstrated by an increase in earlier fetal resorptions. There are no adequate and well-controlled studies in pregnant women. ARDUAN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Obstetrics (cesarean section): There are insufficient data on placental transfer of ARDUAN® and possible related effect(s) upon the neonate following cesarean section delivery. In addition, the duration of action of ARDUAN® exceeds the duration of operative obstetrics (cesarean section). Therefore, ARDUAN® is not recommended for use in patients undergoing C-section.

Pediatric Use: Infants (3 months to 1 year) under balanced anesthesia (2 studies in 52 infants), or halothane anesthesia (1 study in 29 infants), manifest similar dose response to ARDUAN® as do adults on a µg/kg ABW basis. Children (1 to 14 years) under balanced anesthesia (4 studies in 57 children), or halothane anesthesia (2 studies in 29 children), may be less sensitive than adults. These conclusions come from studies involving titrating patient response by the incremental method to approximately 1.2 times ED_{95}. There are no data on either onset time or clinical duration of larger doses in infants or children. There are no data on maintenance dosing in infants and children. Pharmacokinetic studies in infants and children have not been performed, therefore no pharmacokinetic modeling of incremental dosing can be attempted. The use of ARDUAN® in neonates and infants below 3 months of age has not been investigated. Antagonism has not been systematically studied in infants or children. However, usual clinical doses of neostigmine administered following significant levels of spontaneous recovery (recovery of T_1 to more than 50% of control) produced complete antagonism of residual neuromuscular block in less than 10 minutes in the majority of cases.

ADVERSE REACTIONS: The most frequent side effect of non-depolarizing blocking agents as a class is an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. Clinical signs may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea. This may be due to the drug's effect or inadequate antagonism.

The following listings are based upon U.S. clinical studies involving nearly 600 patients utilizing a variety of premedications, varying lengths of surgical procedures, and various anesthetic agents.

Adverse experiences in greater than 1% of cases and judged by the investigator to have a possible causal relationship: clinically significant hypotension (2.5% of cases); clinically significant bradycardia (1.4% of cases).

Adverse experiences in less than 1% of cases and judged by the investigator to have a possible causal relationship:

Cardiovascular: hypertension, myocardial ischemia, cerebrovascular accident, thrombosis, atrial fibrillation, ventricular extrasystole.

Metabolic and Nutritional: increased creatinine, hypoglycemia, hyperkalemia.

Musculoskeletal: muscle atrophy, difficult intubation.

Nervous: hypesthesia, CNS depression.

Respiratory: dyspnea, respiratory depression, laryngismus, atelectasis.

Skin and Appendages: rash, urticaria.

Urogenital system: anuria.

HOW SUPPLIED: 10 mL vials containing 10 mg lyophilized pipecuronium bromide. Boxes of 6 (NDC 0052-0446-36).

Storage: 2°-30°C (36°-86°F). Protect from light.

After Reconstitution: When reconstituted with bacteriostatic water for injection, USP: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.

When reconstituted with sterile water for injection or other compatible IV solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

CAUTION: Federal law prohibits dispensing without prescription.

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2. Foldes FF, Nagashima H, Nguyen HD, Duncalf D, Goldiner PL. Neuromuscular and cardiovascular effects of pipecuronium. *Can J Anaesth.* 1990;37(5): 549-555.
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4. Tassonyi E, Neidheart P, Pittet J-F, Morel DR, Gemperle M. Cardiovascular effects of pipecuronium and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology.* 1988;69(5):793-796.

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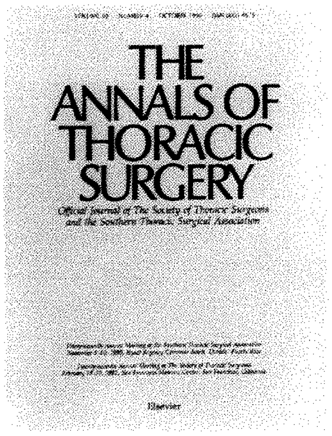

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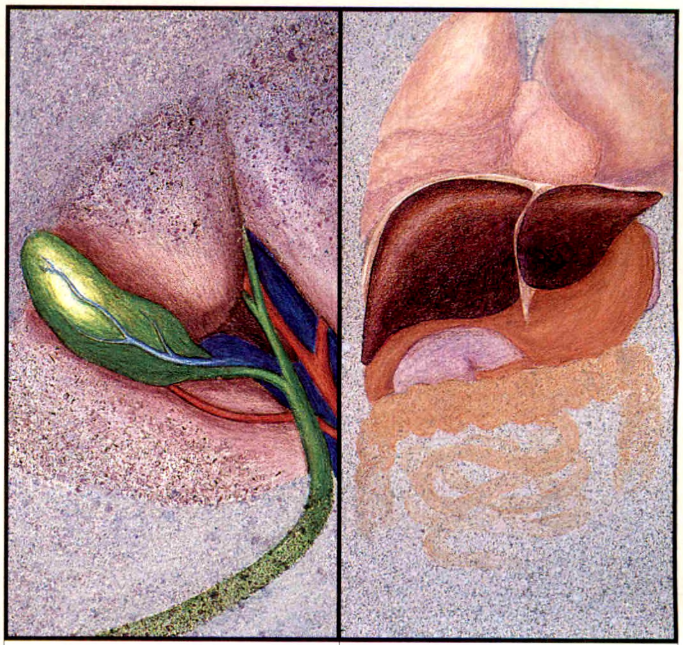
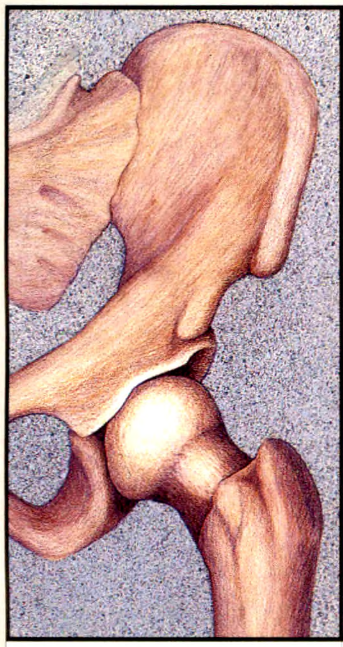
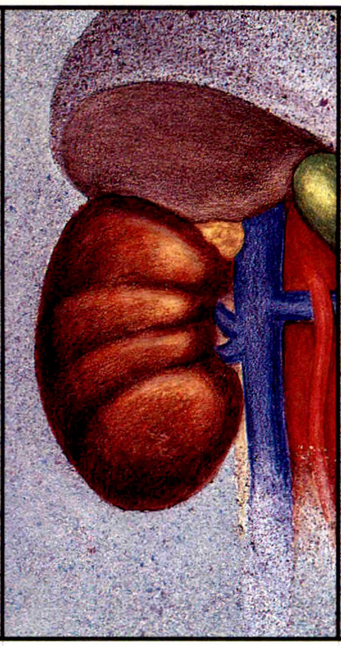
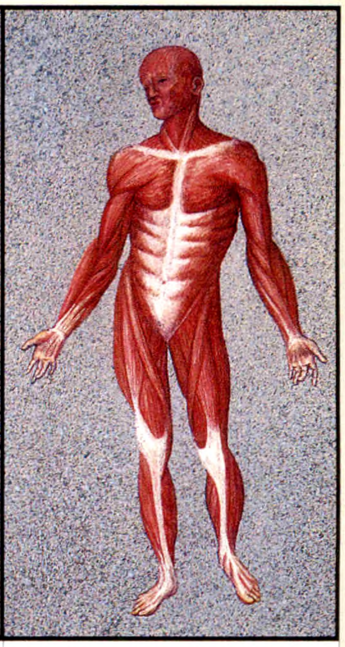
For many procedures
For many reasons



Cholecystectomy	Biliary tract repair
Common patient type Obese	**Common patient type** Both adults and children
Advantage of Tracrium No difference in recovery from neuromuscular blockade between normal and obese patients.[1]	**Advantage of Tracrium** Clinical response unaffected by hepatic function[2] or patient age.[3]

			
Total hip replacement	**Renal surgery**	**Neurosurgery for trauma**	**Everyday procedures**
Common patient type Elderly women and men	**Common patient type** Both adults and children	**Common patient type** Both adults and children	**Common patient type** Average
Advantage of Tracrium Recovery time unaffected by age.[3]	**Advantage of Tracrium** Recovery time unaffected by renal dysfunction.[2]	**Advantage of Tracrium** Effect unchanged by concomitant anticonvulsant medications (phenytoin, carbamazepine).[4,5]	**Advantage of Tracrium** The same reasons Tracrium is ideal for special patient types make it the choice for everyday procedures.

TRACRIUM® INJECTION

(atracurium besylate) 10 mg/mL

For predictable recovery

See brief summary of prescribing information on adjacent page.

TRACRIUM® INJECTION

(atracurium besylate)

Brief Summary
This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia. Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL ampuls and 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS: General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8° C (36° to 46° F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25° C/77° F), use Tracrium Injection within 14 days even if rerefrigerated.

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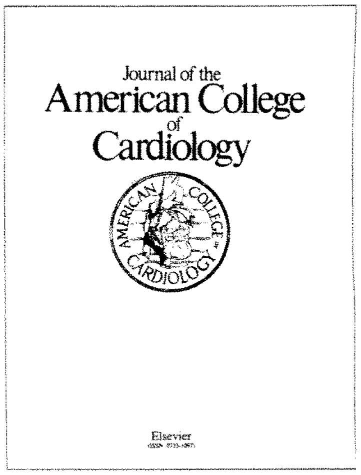

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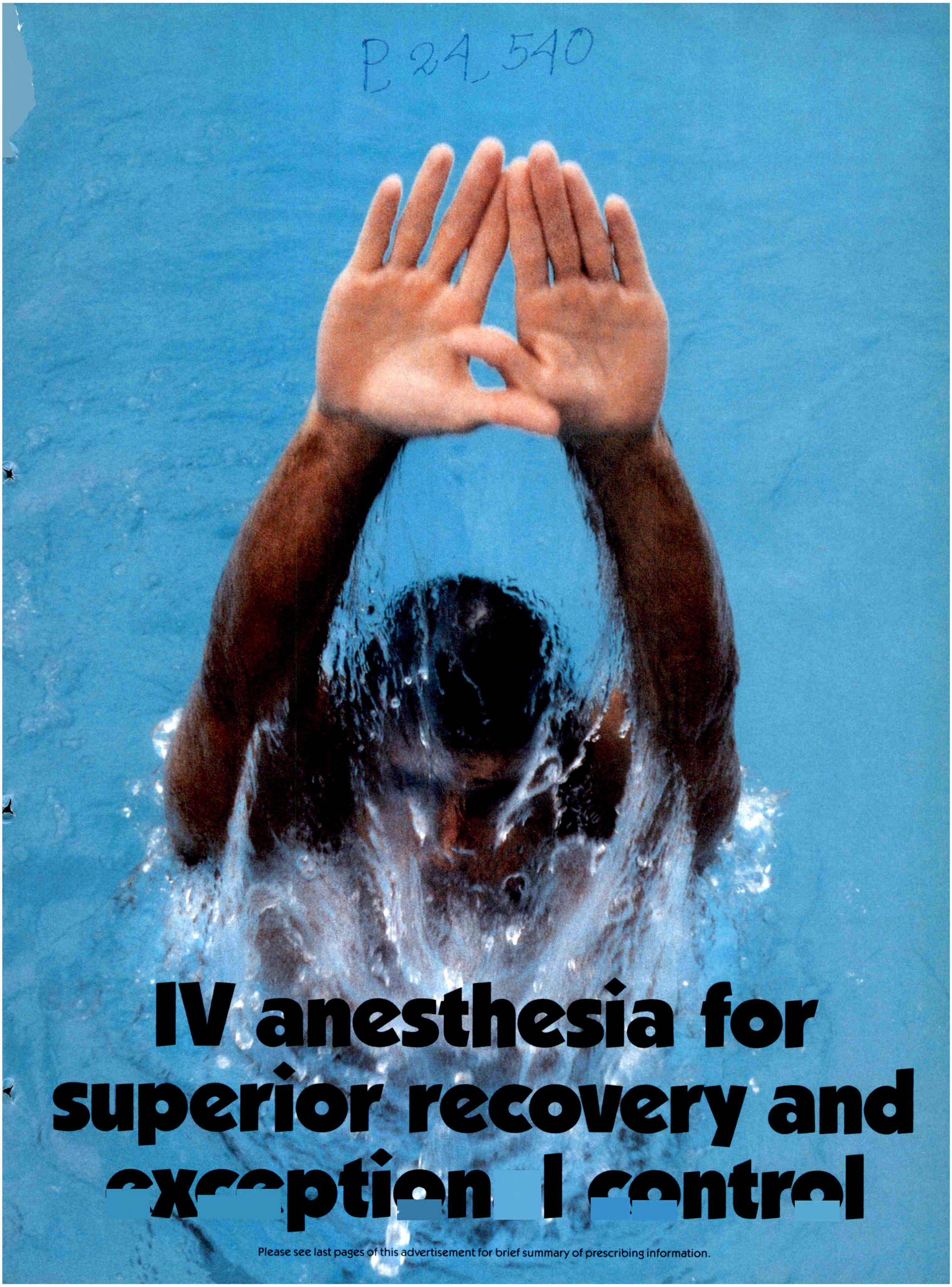

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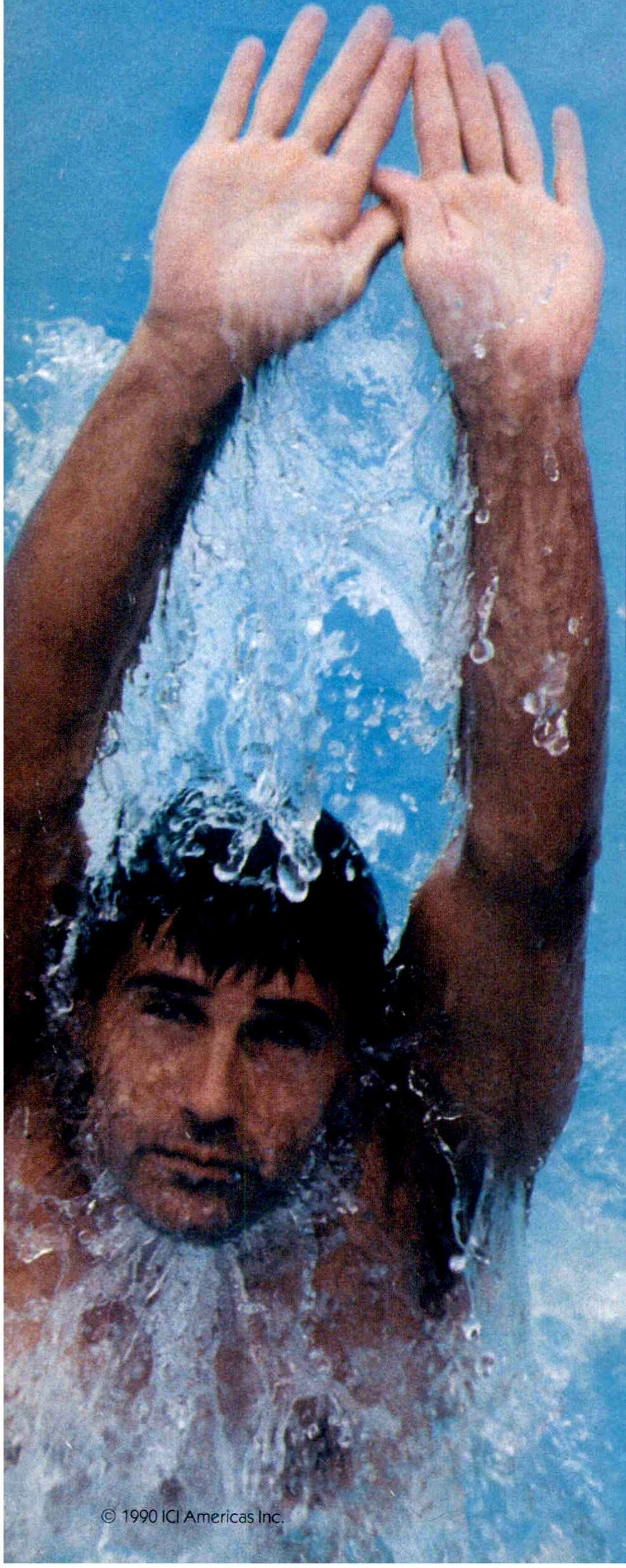
exceptional



Significantly improved speed and quality of recovery compared with thiopental/isoflurane

Mean postanesthesia recovery times (min)[1]

	DIPRIVAN	Thiopental/ isoflurane
Duration of anesthesia	**85***	**57**
Response to commands	3.5*	6.1
Fully oriented	5.5	9.4
Able to tolerate fluids	61*	130
"Ready" for discharge	138*	206

—adapted from Korttila et al, p A564[1]

*Statistically significant ($P < .05$).
Measurements taken from time of discontinuation of all maintenance anesthesia.

- Majority of patients are generally awake, responsive, and oriented within 8 minutes

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recovery and anesthetic control

Significantly less nausea and vomiting than with thiopental/isoflurane

	DIPRIVAN	Thiopental/ isoflurane
Wetchler[2]	(n = 20)	(n = 20)
Nausea/vomiting	20%	65%
Sung et al[3]	(n = 49)	(n = 50)
Nausea/vomiting	8.1%	30%

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

Please see last pages of this advertisement for brief summary of prescribing information.

For induction and maintenance

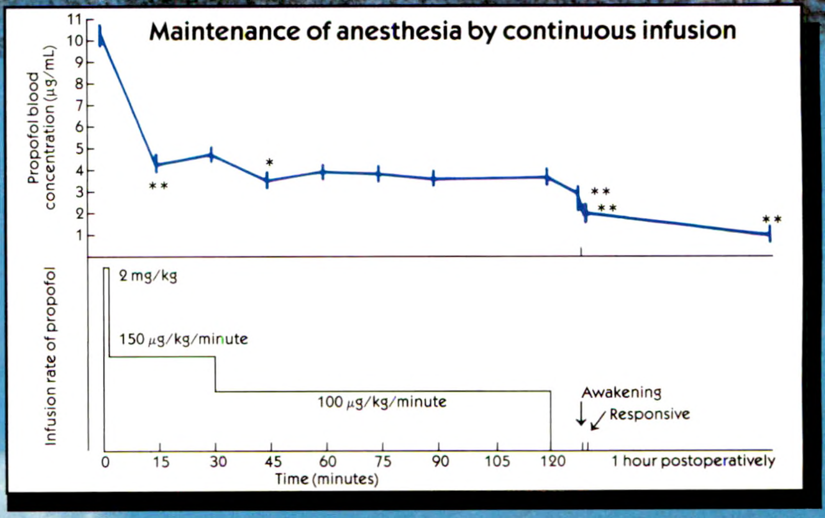
DIPRIVAN®

INJECTION propofol

Superior exceptional

Maintenance of anesthesia as easily controlled as with isoflurane

- Steady state blood concentrations are proportional to rate of administration



—adapted from Herregods et al, p 364[4]

*Significant difference ($P < .05$) from previous value.
**$P < .02$. (Mean and SEM values are shown.)

After a loading dose of 2 mg/kg, anesthesia was maintained with 150 µg/kg/min for 30 minutes—then 100 µg/kg/min for 90 minutes.[4]

- Total body clearance exceeds estimates of hepatic blood flow[5]
- No active metabolites produced

As with most anesthetic agents, clearance rate of DIPRIVAN decreases in elderly patients.

recovery and anesthetic control

Hemodynamic effects are controllable and dose-dependent

- Blood pressure (BP) predictably decreases on induction (sometimes >30%) but is within acceptable ranges for healthy individuals*
- Hemodynamic effects during induction are generally more pronounced than with traditional IV induction agents

After initial decreases in BP following induction, hemodynamics return toward baseline

The cardiovascular effects of DIPRIVAN may be increased in patients who have received sedative or narcotic premedications.[†]

DIPRIVAN is not a narcotic agent
When used with N_2O/O_2 for maintenance, supplementation with IV analgesic agents is generally required; muscle relaxants may also be required.

Strict aseptic techniques must always be maintained while handling DIPRIVAN. DIPRIVAN is a single-use parenteral product and contains no antimicrobial preservatives. DIPRIVAN Injection should be prepared for use just prior to initiation of each individual anesthetic procedure. DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules are opened. Administration should commence promptly and be completed within 6 hours after the ampules have been opened.

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*Elderly, debilitated, and/or hypovolemic patients, and those rated ASA III/IV, may have more profound adverse cardiovascular responses.
[†] Induction dose requirements may be reduced.

Please see last pages of this advertisement for brief summary of prescribing information.

For induction and maintenance

DIPRIVAN®

INJECTION *propofol*

or induction and maintenance

DIPRIVAN®

INJECTION propofol

Superior recovery and exceptional anesthetic control

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

- Significantly improved speed and quality of recovery compared with thiopental/isoflurane
- Significantly less nausea and vomiting than with thiopental/isoflurane
- As convenient and as easily controlled as isoflurane for maintenance of anesthesia

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DIPRIVAN®

INJECTION 10 mg/mL propofol

EMULSION FOR IV ADMINISTRATION

(For full prescribing information, see package insert.)

INDICATIONS AND USAGE: DIPRIVAN Injection is an IV anesthetic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery. DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. (See PRECAUTIONS.) DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN Injection has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. (See PRECAUTIONS.) DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. (See PRECAUTIONS.) DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. (See PRECAUTIONS.) **CONTRAINDICATIONS:** When general anesthesia is contraindicated or in patients with a known hypersensitivity to DIPRIVAN Injection or its components. **WARNINGS:** DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.** DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known. **Strict aseptic techniques must always be maintained while handling DIPRIVAN Injection. The vehicle in DIPRIVAN Injection is capable of supporting rapid growth of microorganisms. (See DOSAGE AND ADMINISTRATION, Handling Procedures.)** **PRECAUTIONS: General:** A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and/or patients with circulatory disorders, and those rated ASA III or IV. (See DOSAGE AND ADMINISTRATION.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis. Since DIPRIVAN Injection is never used alone, an adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the recovery room or to home. When DIPRIVAN Injection is administered to an epileptic patient, there may be a risk of convulsion during the recovery phase. Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous sequelae (phlebitis or thrombosis) have been reported rarely (< 1%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. One accidental intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae. Perioperative myoclonia, rarely including convulsions and opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered. Clinical features of anaphylaxis, which may include bronchospasm, erythema and hypotension, occur rarely following DIPRIVAN Injection administration, although use of other drugs in most instances makes the relationship to DIPRIVAN Injection unclear. DIPRIVAN Injection has no vagolytic activity and has been associated with reports of bradycardia, occasionally profound. The intravenous administration of anticholinergic agents (eg, atropine or glycopyrrolate) should be considered to modify potential increases in vagal tone due to concomitant agents (eg, succinylcholine) or surgical stimuli. **Information for Patients:** Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, may be impaired for some time after general anesthesia. **Drug Interactions:** The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (eg, morphine, meperidine, and fentanyl) and combinations of narcotics and sedatives (eg, benzodiazepines, barbiturates, chloral hydrate, droperidol, etc.). These agents may increase the anesthetic effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output. During maintenance of anesthesia, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anesthesia and may be reduced in the presence of supplemental analgesic agents (eg, nitrous oxide or opioids). The concurrent administration of potent inhalational agents (eg, isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic and cardiorespiratory effects of DIPRIVAN Injection. DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (eg, succinylcholine and nondepolarizing muscle relaxants). No significant adverse interactions with commonly used premedications or drugs used during anesthesia (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Animal carcinogenicity studies have not been performed with propofol. In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using *Salmonella* sp) mutation test, gene mutation/gene conversion using *Saccharomyces cerevisiae*, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test. Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days. **Pregnancy Category B:** Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed. **Labor and Delivery:** DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. **Nursing Mothers:** DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. **Pediatric Use:** DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. **Neurosurgical Anesthesia:** Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures. **ADVERSE REACTIONS:** Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incidence rates. The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 1573 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient. The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency. **Incidence Greater than 1% — All events regardless of causality, derived from clinical trials. Body as a Whole:** Fever. **Cardiovascular:** Hypotension* (see also CLINICAL PHARMACOLOGY), Bradycardia, Hypertension. **Central Nervous System:** Movement*, Headache, Dizziness, Twitching, Bucking/Jerking/ Thrashing, Clonic/Myoclonic Movement. **Digestive:** Nausea**, Vomiting*, Abdominal Cramping. **Injection Site:** Burning/Stinging**, Pain**, Tingling/Numbness, Coldness. **Respiratory:** Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY). **Skin and Appendages:** Flushing. Incidence of unmarked events is 1%-3%; *3% to 10%; **10% or greater. **Incidence Less than 1% — Causal Relationship Probable** (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*) **Body as a Whole:** Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. **Cardiovascular:** Tachycardia, Premature Ventricular Contractions, Premature Atrial Contractions, Syncope, Abnormal ECG, ST Segment Depression. **Central Nervous System:** Shivering, Somnolence, Hypertonia/Dystonia, Paresthesia, Tremor, Abnormal Dreams, Agitation, Confusion, Delirium, Euphoria, Fatigue, Moaning, Rigidity. **Digestive:** Hypersalivation, Dry Mouth, Swallowing. **Injection Site:** Discomfort, Phlebitis, Hives/Itching, Redness/Discoloration. **Musculoskeletal:** Myalgia. **Respiratory:** Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia. **Skin and Appendages:** Rash, Urticaria. **Special Senses:** Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus. **Urogenital:** Urine Retention, *Green Urine.* **Incidence Less than 1% — Causal Relationship Unknown** (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*) **Cardiovascular:** Arrhythmia, Bigeminy, Edema, Ventricular Fibrillation, Heart Block, *Myocardial Ischemia.* **Central Nervous System:** Anxiety, Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures, *Opisthotonus.* **Digestive:** Diarrhea. **Respiratory:** Laryngospasm. **Skin and Appendages:** Diaphoresis, Pruritus, *Conjunctival Hyperemia.* **Special Senses:** Ear Pain, *Nystagmus.* **Urogenital:** Abnormal Urine. **DRUG ABUSE AND DEPENDENCE:** None known. **OVERDOSAGE:** To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. If accidental overdosage occurs, DIPRIVAN Injection administration should be discontinued immediately. Overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require repositioning of the patient by raising the patient's legs, increasing the flow rate of intravenous fluids and administering pressor agents and/or anticholinergic agents. The intravenous LD_{50} values are 53 mg/kg in mice and 42 mg/kg in rats. **DOSAGE AND ADMINISTRATION: Induction:** Dosage should be individualized and titrated to the desired effect according to the patient's age and clinical status. Most adult patients under 55 years of age and classified ASA I and II are likely to require 2.0 to 2.5 mg/kg of DIPRIVAN Injection, for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia. It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated, hypovolemic patients and/or those in ASA Physical Status Classes III or IV. These patients may be more sensitive to the effects of DIPRIVAN Injection; therefore, the dosage of DIPRIVAN Injection should be decreased in these patients by approximately 50% (20 mg every 10 seconds) according to their conditions and responses. (See PRECAUTIONS, and DOSAGE GUIDE.) Additionally, as with most anesthetic agents, the effects of DIPRIVAN Injection may be increased in patients who have received intravenous sedative or narcotic premedications shortly prior to induction. **Maintenance:** Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections. When administering DIPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps or volumetric pumps be used to provide controlled infusion rates. **Continuous Infusion:** DIPRIVAN Injection 0.1 to 0.2 mg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction injection higher rates of infusion are generally required (0.15 to 0.20 mg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30%- 50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as a narcotic, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses. For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN Injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile. Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance in order to optimize recovery times. **Intermittent Bolus:** Increments of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia. DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See Drug Interactions.)

DOSAGE GUIDE

INDICATION	DOSAGE AND ADMINISTRATION
Induction	Dosage should be individualized. **Adults:** Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). **Elderly, Debilitated, Hypovolemic, and/or ASA III or IV Patients:** Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).
Maintenance Infusion	**Variable rate infusion**—titrated to the desired clinical effect. **Adults:** Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Generally, 0.05 to 0.1 mg/kg/min (3 to 6 mg/kg/h).
Intermittent Bolus	Increments of 25 mg to 50 mg, as needed.

Compatibility and Stability: DIPRIVAN Injection should not be mixed with other therapeutic agents prior to administration. **Dilution Prior to Administration:** When DIPRIVAN Injection is diluted prior to administration, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic.) **Administration into a Running IV Catheter:** Compatibility of DIPRIVAN Injection with the coadministration of blood/serum/plasma has not been established. (See WARNINGS.) DIPRIVAN Injection has been shown to be compatible with the following intravenous fluids when administered into a running IV catheter: 5% Dextrose Injection, USP; Lactated Ringers Injection, USP; Lactated Ringers and 5% Dextrose Injection; 5% Dextrose and 0.45% Sodium Chloride Injection, USP; 5% Dextrose and 0.2% Sodium Chloride Injection, USP. **Handling Procedures:** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. DIPRIVAN Injection must not be administered through a microbiological filter because this could restrict the flow of DIPRIVAN and/or cause the breakdown of the emulsion. Do not use if there is evidence of separation of the phases of the emulsion. Strict aseptic techniques must always be maintained during handling as DIPRIVAN Injection is a single-use parenteral product and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms. DIPRIVAN Injection should be prepared for use just prior to initiation of each individual anesthetic procedure. DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules or vials are opened. When using vials with volumetric infusion devices insert sterile vent spike through rubber stopper and immediately connect IV line. Administration should commence promptly and be completed within 6 hours after the ampules or vials have been opened. DIPRIVAN Injection should be prepared for single patient use only and any unused portions of DIPRIVAN Injection, reservoirs, IV lines or solutions containing DIPRIVAN Injection must be discarded at the end of the anesthetic procedure. Failure to follow aseptic handling procedures may result in microbial contamination causing fever and/or other adverse consequences which could lead to life-threatening illness. *Aseptic Technique* for Handling DIPRIVAN Injection Ampules:* • Wear clean garments. • Wash hands and fingernails using an antimicrobial handwash. • When appropriate, wear sterile gloves, mask and hair cover. • Disinfect neck surface of ampule using 70% isopropyl alcohol. Swab neck of ampule by wiping in one direction and let dry. • Protect fingers and hands by using sterile gauze when opening the ampule. • Withdraw DIPRIVAN Injection into a sterile syringe. • Immediately replace needle cap and discard ampule. • Label syringe with appropriate information, including date, time and patient name. • Administer promptly. • Discard any unused DIPRIVAN Injection and reservoirs, IV lines, or solutions containing DIPRIVAN Injection at the end of the anesthetic procedure or within 6 hours—whichever occurs sooner. *Aseptic Technique* for Handling DIPRIVAN Injection Vials (and for Use With Volumetric Infusion Devices):* • Wear clean garments. • Wash hands and fingernails using an antimicrobial handwash. • When appropriate, wear sterile gloves, mask and hair cover. • Remove metal cap from vial. • Disinfect rubber stopper of vial using 70% isopropyl alcohol. Wipe in one direction and let dry. • Insert sterile vent spike through rubber stopper and remove luer cap. • Connect a sterile syringe(s) to vent spike and withdraw entire contents; (Or when using volumetric infusion devices, aseptically connect IV line to vent spike). • Immediately cap syringe(s) with sterile closure(s) and discard vial and vent spike. • Label syringe(s) (or vial when using volumetric infusion devices) with appropriate information, including date, time and patient name. • Administer promptly. • Discard any unused DIPRIVAN Injection and reservoirs, IV lines, or solutions containing DIPRIVAN Injection at the end of the anesthetic procedure or within 6 hours—whichever occurs sooner. *These techniques are not intended to preempt more stringent, established institutional guidelines for the aseptic handling and administration of sterile parenteral drug products. **HOW SUPPLIED:** DIPRIVAN Injection is available in ready to use 20 mL ampules and 50 mL infusion vials containing 10 mg/mL of propofol.

20 mL ampules (NDC 0038-0290-20) 50 mL infusion vials (NDC 0038-0290-50)

Store below 22°C (72°F). Do not store below 4°C (40°F). Refrigeration is not recommended. Protect from light. Shake well before use.

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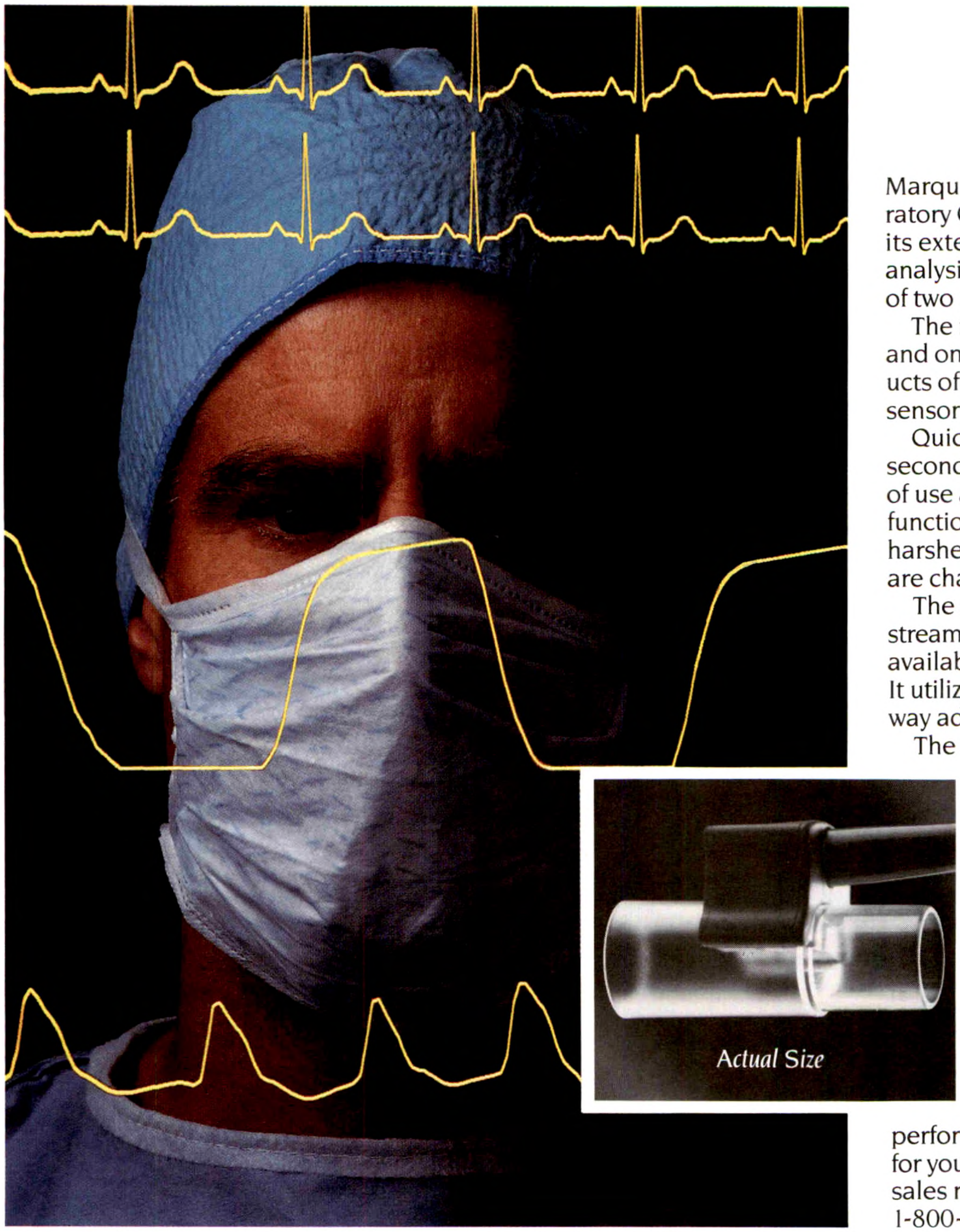

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Needles: A Sticky Situation for U.S. Healthcare.

Healthcare workers in Americ are facing an epidemic problem - needle sticks. Each year thousand of healthcare workers ar accidentally stuck in hospitals, nursing hom nics and i general practice. se needle sticks can lead to very ous infections, with at least 20 ent pathogens having been ide as transmitt in this way.

In fact, t ew Englan Journal of M orted in i August 4th iss) that as ma as 12,000 h e provide contract hepa each year. large segmen t universe infected by ac needle stick The seriousne can be seen this statistic: accounts f 200 to 300 deaths a year to healthcare providers. And the number is growing every year. Add to this fact that the danger is now unded by the AIDS virus and can see just how critical inating needles truly is.

According to the Center for ease Control in Atlanta, rgia, a healthcare professional s a one in 200 chance of tracting AIDS from a aminated needle and industry ces report that over 800,000 le sticks occur each year in als alone. With these kinds of it is no wonder that the care professions are seeking ons to this massive problem.

To look at the problem from er point of view, consider the f this epidemic. It is estimated etween $400 million and $1.0 n is spent per year in direct arising from needle sticks and this range does not include treatment or loss of work. In other words, aside from the human suffering associated with the infamous needle stick, the pocket book is infected, too.

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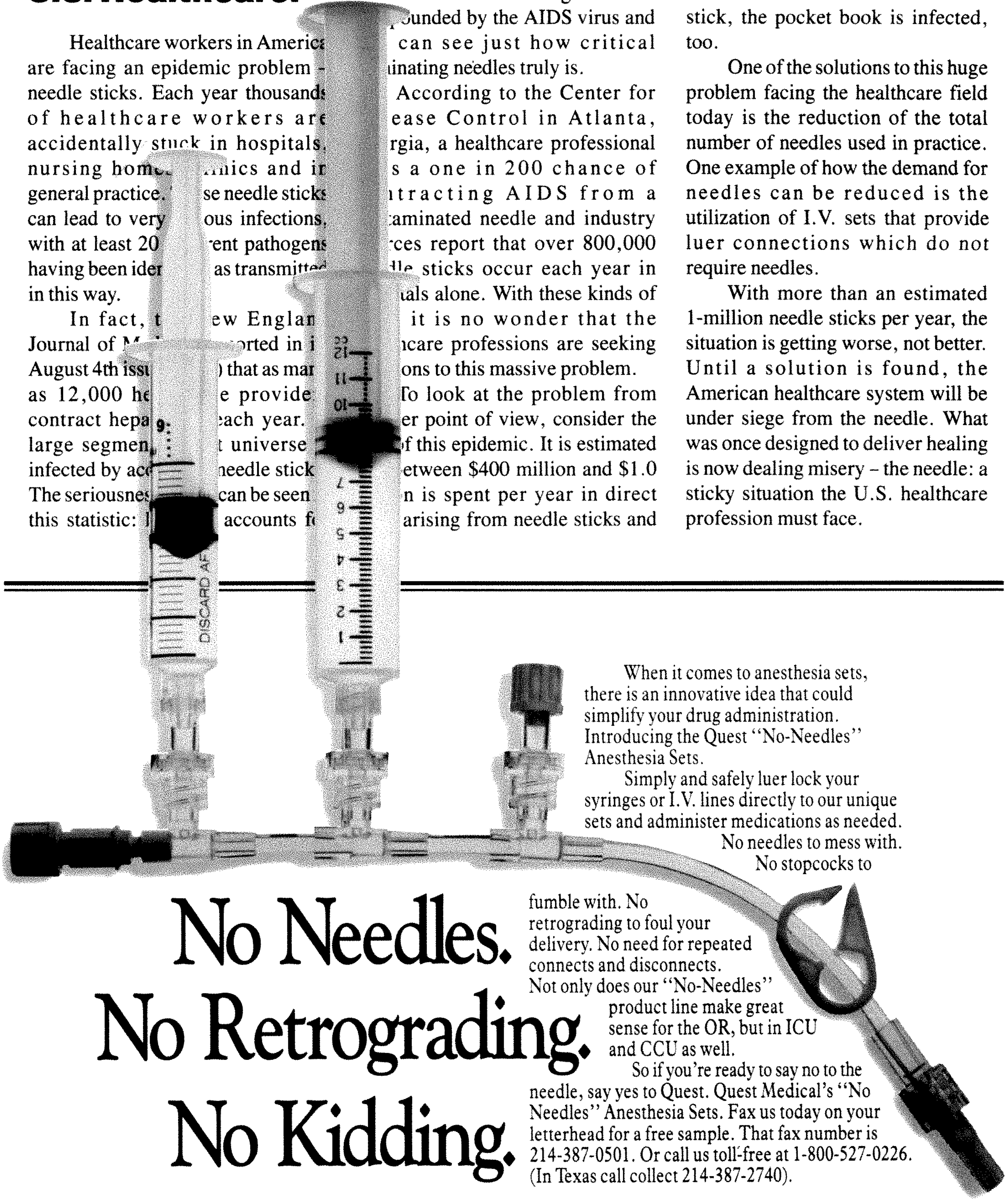

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		SELDON MEMORIAL LECTURE – JEROME H. MODELL, MD **CONTINENTAL BALLROOM 5**								10:30-12:00 pm
		LOCAL	PHARM		PEDS	VAN AKEN SAVARESE	ASA Practice Guidelines M. Roizen	Introduction to Statistics PACE		1:30-3:00 pm
		CRIT CARE	N-MUSC		ED/SAF	BROADMAN TINKER				3:30-5:00 pm
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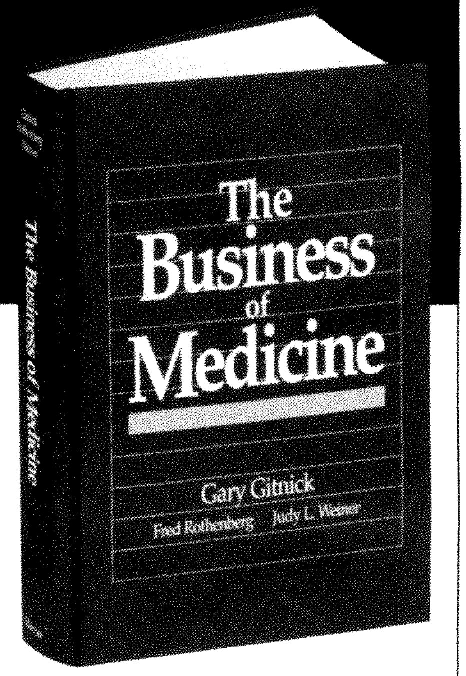
The complete guide to managing a successful practice

The Business of Medicine



Edited by
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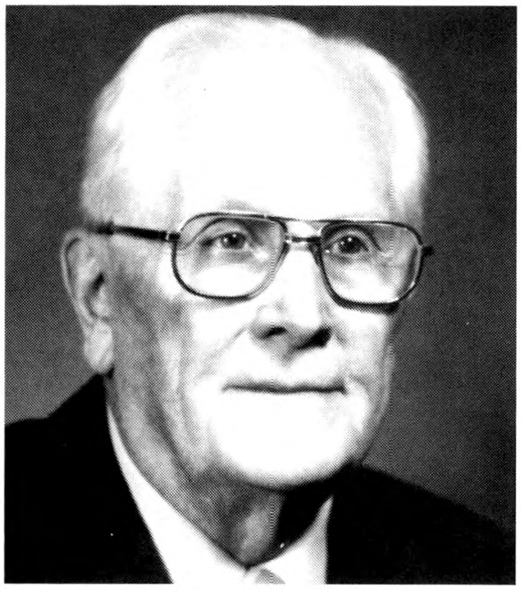
Dr. Modell's 34-year career in anesthesiology began at the U.S. Naval Hospital in St. Albans, New York. At age 36 he assumed the Chairmanship of the Anesthesia Department at the University of Florida where he continues to promote excellence in clinical care, medical education, and research. Dr. Modell has been very active in organized anesthesia at the national and local levels. He has served as president of his state society, the Association of University Anesthesiologists, and the Society of Academic Anesthesia Chairmen. As the economics and politics of medicine have expanded, his active role has earned him the reputation as a pacesetter in today's medical community.

Jerome H. Modell, MD, Chairman, Department of Anesthesiology and Senior Associate Dean for Clinical Affairs, University of Florida College of Medicine, Gainesville, Florida



T. H. Seldon, MD, FFARCS(I)
(1905–1991)

The Lecture to be given by Dr. Modell is the tenth such to honor Dr. T. H. ``Harry" Seldon, who served as Editor of *Anesthesia & Analgesia* for 23 years ending in 1977. Dr. Seldon passed away in October 1991 at the age of 86.

IARS 66TH CONGRESS

Review Course Lectures

Saturday, March 14, 1992

8:30 AM *Update on Anesthesia for Trauma,* **BRUCE F. CULLEN, MD,** Professor of Anesthesiology, Anesthesiologist-in-Chief, University of Washington School of Medicine, Harborview Medical Center, Seattle, Washington

9:15 AM *Cardiopulmonary Bypass and the Brain,* **DONALD S. PROUGH, MD,** Professor and Chairman, Department of Anesthesiology, University of Texas Medical Branch, Galveston Texas; **ANNE T. ROGERS, MBChB, FRCPC,** Assistant Professor of Anesthesia; **WILLIAM E. JOHNSTON, MD,** Associate Professor of Anesthesia, Bowman Gray School of Medicine, Wake Forest University Medical Center, Winston-Salem, North Carolina

10:30 AM *The Impact of AIDS on the Practice of Anesthesia,* **RONALD D. MILLER, MD,** Professor and Chairman, Department of Anesthesia; Professor of Pharmacology, University of California, San Francisco, California

11:15 AM *Anesthetic Liability: What It Is and What It Isn't,* **ROBERT A. CAPLAN, MD,** Staff Anesthesiologist, Virginia Mason Medical Center; Associate Clinical Professor of Anesthesiology, University of Washington, Seattle, Washington

1:30 PM *Practical Pharmacokinetics for the Clinician,* **WALTER S. NIMMO, BSc, MD, FRCP, FFARCS, FFARACS,** Director, Inveresk Clinical Research, Edinburgh; Fellow, Department of Anaesthesia, Royal Infirmary, Edinburgh, Scotland

2:15 PM *Intravenous Anesthetic Drug Delivery in Anesthesia,* **J. GERALD REVES, MD,** Professor and Chairman, Department of Anesthesiology; **JAMES R. JACOBS, PhD,** Assistant Professor of Anesthesiology and Biomedical Engineering; **PETER S.A. GLASS, MD,** Assistant Professor of Anesthesiology, Duke University School of Medicine, Durham, North Carolina

3:30 PM *Post-Op Pain Relief: Does the Technique Matter?,* **PHILLIP O. BRIDENBAUGH, MD,** Professor and Chairman, Department of Anesthesia, University of Cincinnati College of Medicine, Cincinnati, Ohio

4:15 PM *New Techniques in the Management of Septic Shock,* **RONALD G. PEARL, MD,** Assistant Professor, Department of Anesthesiology, Stanford University Medical Center, Palo Alto, California

Sunday, March 15, 1992

8:30 AM *Complications of Regional Anesthesia,* **MICHAEL F. MULROY, MD,** Staff Anesthesiologist, Department of Anesthesiology, Virginia Mason Medical Center, Seattle, Washington

9:15 AM *The Patient With Congenital Heart Disease for Non-Cardiac Surgery: Anesthesia for the Reconstructed and the Unreconstructed Heart,* **PAUL R. HICKEY, MD,** Associate Professor of Anaesthesia, Harvard Medical School; Director, Cardiac Anaesthesia Service, The Children's Hospital, Boston, Massachusetts

1:30 PM *Anesthetic Management of the Patient With Head Injury,* **HUGO VAN AKEN, MD,** Professor and Chairman, Department of Anesthesiology; **J. VAN HEMELRIJCK, MD,** Assistant Professor of Anesthesiology, University Hospitals, Katholieke Universiteit, Leuven, Belgium

2:15 PM *New, Newer, Newest, and Imaginary Muscle Relaxants,* **JOHN J. SAVARESE, MD,** The Joseph F. Artusio Jr. Professor and Chairman, Department of Anesthesiology, Cornell University Medical College, New York, New York

3:30 PM *Regional Anesthesia in Children,* **LYNN M. BROADMAN, MD,** Professor of Anesthesiology and Pediatrics, Vice Chairman, Department of Anesthesiology, West Virginia University School of Medicine, Morgantown, West Virginia

4:15 PM *Quality: A Lesson From the Japanese,* **JOHN H. TINKER, MD,** Professor and Head; **NIELS F. JENSEN, MD,** Assistant Professor of Anesthesia, Department of Anesthesia, University of Iowa College of Medicine, Iowa City, Iowa

Review Course Lectures (cont.)

Monday, March 16, 1992

8:30 AM *Current Status of Sevoflurane and Desflurane,* **EDMOND I. EGER II, MD,** Professor and Vice Chairman for Research, Department of Anesthesia, University of California, San Francisco, California

9:15 AM *Preserving Renal Function During Surgery,* **SIMON GELMAN, MD, PhD,** Professor of Anesthesiology, Department of Anesthesiology, Professor of Physiology and Biophysics, The University of Alabama at Birmingham, Birmingham, Alabama

10:30 AM *Anesthesia for Thoracic Surgery,* **GREGG S. HARTMAN, MD,** Associate Professor, Department of Anesthesiology, Cornell University Medical College, New York, New York

11:15 AM *Cardiac Physiology for the Clinician,* **DAVID C. WARLTIER, MD, PhD,** Professor and Vice Chairman for Research, Department of Anesthesiology; Professor of Cardiology and Pharmacology, Medical College of Wisconsin, Milwaukee, Wisconsin

1:30 PM *Controversies in Obstetric Anesthesia,* **RICHARD J. PALAHNIUK, MD,** Professor and Head, Department of Anesthesiology, University of Minnesota, Minneapolis, Minnesota

2:15 PM *Ambulatory Anesthesia,* **PATRICIA A. KAPUR, MD,** Associate Professor,Department of Anesthesiology, University of California, Los Angeles Center for the Health Sciences, Los Angeles, California

3:30 PM *Cerebral Ischemia: State of the Art Management,* **JOHN C. DRUMMOND, MD, FRCPC,** Associate Professor, Department of Anesthesiology, University of California, San Diego; Staff Anesthesiologist, VA Medical Center, San Diego, California

4:15 PM *Anesthetic Delivery Systems in the 1990's,* **THEODORE H. STANLEY, MD,** Professor of Anesthesiology; Michael A. Ashburn, MD, Assistant Professor of Anesthesiology, Department of Anesthesiology, University of Utah Health Sciences Center, Salt Lake City, Utah

Tuesday, March 17, 1992

8:30 AM *Oximetry, Capnography, and Other Non-Invasive Wizardry,* **KEVIN K. TREMPER, MD, PhD,** Professor and Chairman, Department of Anesthesiology, University of Michigan School of Medicine, Ann Arbor, Michigan

9:15 AM *Coagulation System: Intraoperative Measurement and Management,* **BRUCE D. SPIESS, MD,** Associate Professor of Anesthesiology, Chief of the Division of Cardiothoracic Anesthesia, Associate Chief of Anesthesia Clinical Services, University of Washington Medical Center, Seattle, Washington

10:30 AM *Anesthetic Management of the High Risk Obstetrical Patient,* **MIECZYSLAW FINSTER, MD,** Professor of Anesthesiology, Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, New York, New York

11:15 AM *Anesthesia for the Patient With Endocrine Disease,* **ROBERT K. STOELTING, MD,** Professor and Chairman, Department of Anesthesia, Indiana University School of Medicine, Indianapolis, Indiana

Tutorials, Panels, Luncheons

TUTORIALS

Saturday, March 14, 1992

1:30 - 3:00 **Regional Anesthesia**
A. R. Brown, MD, Columbia University College of Physicians and Surgeons, New York, New York

1:30 - 3:00 **Fiberoptic Bronchoscopy**
J. T. Roberts, MD, Massachusetts General Hospital, Boston, Massachusetts

3:30 - 5:00 **How to Publish**
D. R. Bevan, MB, University of British Columbia, Vancouver, BC, Canada

Sunday, March 15, 1992

8:30 - 10:00 **Transesophageal Echocardiography**
M. K. Cahalan, MD, University of California, San Francisco, California

8:30 - 10:00 **Fiberoptic Bronchoscopy**
J. T. Roberts, MD, Massachusetts General Hospital, Boston, Massachusetts

1:30 - 5:00 **Introduction to Statistics**
N. L. Pace, MD, University of Utah College of Medicine, Salt Lake City, Utah

Monday, March 16, 1992

8:30 - 10:00 **Transesophageal Echocardiography**
M. K. Cahalan, MD, University of California, San Francisco, California

8:30 - 10:00 **Fiberoptic Bronchoscopy**
J. T. Roberts, MD, Massachusetts General Hospital, Boston, Massachusetts

10:30 - 12:00 **Vasoactive Drugs**
N. W. Lawson, MD, University of Texas Medical Branch, Galveston, Texas

1:30 - 3:00 **Regional Anesthesia**
A. R. Brown, MD, Columbia University College of Physicians and Surgeons, New York, New York

1:30 - 3:00 **Fiberoptic Bronchoscopy**
J. T. Roberts, MD, Massachusetts General Hospital, Boston, Massachusetts

3:30 - 5:00 **Patient with Non-Coronary Heart Disease,**
S. J. Thomas, MD, New York Hospital-Cornell Medical College, New York, New York

PANELS

Saturday, March 14, 1992

8:30 - 12:00 **Does the Choice of Anesthetic Technique Really Matter?**
K. J. Tuman, MD, Rush-Presbyterian-St. Lukes Medical Center, Chicago, Illinois

1:30 - 5:00 **ASA Practice Guidelines for Difficult Airway Management**
R. A. Caplan, MD, Virginia Mason Medical Center, Seattle, Washington

Sunday, March 15, 1992

1:30 - 5:00 **ASA Practice Guidelines for Pulmonary Artery Catheterization Monitoring**
M. F. Roizen, MD, University of Chicago, Chicago, Illinois

Monday, March 16, 1992

8:30 - 12:00 **Clinical Cases from the Real World**
J. L. Waller, MD, Emory University Hospital, Atlanta, Georgia

Tuesday, March 17, 1992

8:30 - 12:00 **Critical Incidents in Anesthesia: Analysis and Prevention**
D. M. Gaba, MD, V.A. Medical Center, Stanford, California

LUNCHEONS

Saturday, March 14, 1992

12:00 - 1:30 **Cardiopulmonary Bypass in the 90s**
J. G. Reves, MD, Duke University School of Medicine, Durham, North Carolina
J. H. Tinker, MD, University of Iowa Hospitals & Clinics, Iowa City, Iowa

Sunday, March 15, 1992

12:00 - 1:30 **Pain Management: Who to, How to, and Payment for**
P. O. Bridenbaugh, MD, University of Cincinnati College of Medicine, Cincinnati, Ohio
L. C. Novak, MD, Wenatchee Anesthesia Associates, Wenatchee, Washington

Monday, March 16, 1992

12:00 - 1:30 **Legislative/Economic Update**
G. W. N. Eggers, Jr, MD, President, American Society of Anesthesiologists, University of Missouri Medical Center, Columbia, Missouri
A.C. Lang, Director, Office of Governmental Affairs, American Society of Anesthesiologists, Washington, D.C.
S.J. Thomas, MD, Chairman, ASA Committee on Economics, New York, New York

Registration

PRE-REGISTRATION: Registration cards and checks at the lower pre-registration rates shown below must be received in Cleveland by March 4, 1992. Pre-registrants can pick up their meeting badges and meeting materials at the IARS registration desk at the San Francisco Hilton beginning at 1 PM on Friday, March 13. Registration cancelled by March 4 will be refunded in full; thereafter, a $50 cancellation fee will apply.

REGISTRATION AT THE MEETING: If you prefer to register at the meeting, you may do so beginning at 1 PM on Friday, March 13 at the higher on-site rates shown below.

IARS members who register at the meeting should bring their IARS membership cards. Nonmember residents in training and nurse anesthesia students must bring certifying letters from their program directors to register at the reduced rates shown.

MEETING MATERIALS: Abstracts of the scientific papers and posters presented at the meeting are published as a Supplement to the February 1992 issue of ***Anesthesia & Analgesia***. The Review Course Lectures will be a separate publication mailed with the April 1992 journal. Copies of both publications will be included in the meeting packet of all scientific meeting registrants.

The IARS acknowledges with thanks: Major funding from **Anaquest Inc., A Division of BOC, Inc.**, that enables us to make the Review Course Lectures booklet available to all Society members and the support of **Burroughs Wellcome Co.** in underwriting publication of the Abstracts Supplement.

REGISTRATION FEES	Paid by March 4	Paid at Meeting
IARS Members and Associate Members	$325	$350
IARS Educational Members	NO FEE	NO FEE
*New IARS Members and Associate Members	$420 ($445**)	$445 ($470**)
*New IARS Educational Members	NO FEE	NO FEE
*Non-IARS Members	$500	$525
*Non-IARS Members (residents, nurse trainees)	$50	$50

*Please see following page for membership/registration information.
**Rate for members outside of US–in US$.
NOTE: There is no fee for designated program speakers, poster presenters, scientific and technical exhibitors; designated medical media; or spouses of registrants unless they are attending for professional credit.

Hotel Information

The **HEADQUARTERS HOTEL** for all meetings and exhibits is the San Francisco Hilton on Hilton Square where the IARS has blocked the major portion of convention-rate sleeping rooms. The largest hotel on the West Coast, the San Francisco Hilton was recently renovated and expanded to include the addition of an executive business center and a professionally staffed fitness center. The hotel has five restaurants and is conveniently located just steps from the financial district, Union Square, cable cars, theaters, Chinatown, and more.

A small block of rooms is also available at the nearby **Handlery Union Square Hotel** at a reduced daily rate. One night deposit (check, major credit card) must accompany each reservation. The cut-off date for reservations at convention rates is **February 13, 1992**; thereafter, rooms at convention rates are on a space-available basis only.

Continuing Education Credit

AMA: The International Anesthesia Research Society is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. The IARS certifies that the 66th Congress meets the criteria for 27 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association.

AANA: CRNAs must secure post-meeting approval from the AANA. Appropriate forms will be available at the meeting.

Special Air Fares

Delta and United Airlines will offer **special discounted rates** to IARS meeting registrants for round-trip travel to San Francisco. Reservation can be made directly, or through your travel agent – but must be made through the telephone numbers shown below and should mention the IARS meeting and the reference numbers shown.

DELTA	UNITED
1-800-241-6760	1-800-521-4041
File No. P-0095	Account 510XA

IARS MEMBERSHIP

FOR YOUR IN-TRAINING AND CONTINUING MEDICAL EDUCATION

The International Anesthesia Research Society is a nonprofit, scientific and educational corporation of the State of Ohio, founded in 1922 "to foster progress and research in anesthesia." To this end, the IARS

Publishes the oldest journal in the specialty, *Anesthesia & Analgesia*

Sponsors an annual scientific meeting (Congress) which is held in March

Funds projects in anesthesia-related research, clinical care, education, and administration through the B.B. Sankey Anesthesia Advancement Award

Membership in the IARS is voluntary; it is also separate and distinct from membership in any other local, state, or national anesthesia organization. Membership is open to individuals who qualify in the various categories shown below. All memberships include a monthly subscription to *Anesthesia & Analgesia*. Members and Associate Members are entitled to a reduced registration fee at the IARS annual meeting; Educational Members pay no registration fee. Only IARS members may apply for the B.B. Sankey Anesthesia Advancement Award.

MEMBERSHIP CATEGORIES

MEMBERSHIP: Open to individuals with doctorate degrees who are licensed to practice in the medical, osteopathic, dental, or veterinary medicine fields (i.e., MD, MB, DO, DDS, DVM); and to individuals with doctorate degrees (PhD) in any scientific discipline who are engaged in academic, private, or commercial research.

ASSOCIATE MEMBERSHIP: Open to individuals in the allied health professions who are certified by their professional accrediting organization as nurse anesthetists (CRNA), respiratory therapists or technicians (RRT or CRTT), physician assistants (PA, MMS), and other allied health professionals in anesthesia-related practice.

Annual (1992 Calendar Year) Dues for Members and Associate Members: $95 ($120 Foreign).

EDUCATIONAL MEMBERSHIP: Open (with certification by program director) to doctors (interns/residents) enrolled in anesthesiology training programs; nurses enrolled in nurse anesthesia schools; students enrolled in programs leading to certification as physician assistants, respiratory therapists, or technicians.

Annual Dues for Educational Members:

2 Years beginning July 1991—$98 ($145 Foreign)
3 Years beginning July 1991—$148 ($220 Foreign)
4 Years beginning July 1991—$198 ($295 Foreign)

2 Years beginning January 1992—$100 ($150 Foreign)
3 Years beginning January 1992—$150 ($225 Foreign)
4 Years beginning January 1992—$200 ($300 Foreign)

SPECIAL NOTE TO NON-IARS MEMBERS WHO PLAN TO ATTEND THE 66th CONGRESS

If you qualify for Membership or Associate Membership:

You may become an IARS member and register for the meeting for a single total fee of $420, if completed membership application, registration card, and check are sent to Cleveland office by March 4, 1992. At the meeting this charge will be $445. (Foreign members add $25 in each case.)

If you do not wish to become an IARS member, the registration fee is $500 if paid by March 4 and $525 if paid at the meeting.

If you qualify for Educational Membership:

You may become a member, and receive complimentary registration, if you submit a certified Educational Membership application, a check to cover membership term (2, 3, 4 years), and a registration card either by March 4 or at the meeting. Membership dues amounts are shown on application.

If you do not wish to become an Educational Member, the registration fee is $50 (before or at the meeting) and must include letter certifying your current enrollment in an anesthesia training program.

The B.B. Sankey Anesthesia Advancement Award

Sunday, March 15, 1992
Award Presentations 10:30–11:00 AM
Continental Ballroom 5

1992 AWARDS: Award recipient(s) will be announced at this meeting. Since its inception in 1983, over $900,000 has been distributed to fund 37 projects—including six awards in 1991 to:

Mitchell F. Berman, MD
Columbia University

Alberto J. de Armendi, MD, AM
Massachusetts General Hospital

Stephen W. King, PhD, MD
University of California at San Francisco

Pontus Östman, MD
University of Iowa

Mark S. Scheller, MD
University of California at San Diego

Margaret M. Sedensky, MD
Case Western Reserve University School of Medicine

1993 AWARDS: IARS members are invited to submit applications for this Award which will be announced at the 67th Congress to be held in San Diego, March 19–23, 1993. This broadly based Award considers projects in the fields of anesthesia-related research, clinical care, administration, or education. Application forms will be available from the IARS Cleveland office in May 1992.

The IARS established the Anesthesia Advancement Award to honor Dr. Sankey when he retired as Trustee and Executive Secretary of the Society in 1983. At his retirement from practice on November 1, 1989, he completed 52 years of service to the specialty as a clinical practitioner; an active member and officer of the Cleveland and Ohio societies; a founder of the Anesthesia Foundation; and president of the ASA in 1955.

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THE ADVANTAGE OF CO-INDUCTION

Anesthetic Synergy

VERSED first, followed by a second anesthetic

When given first, a small dose of VERSED® (midazolam HCl/Roche) may lower the induction ED_{50} of barbiturates or narcotics up to 75%.[1-4] This synergistic effect appears to result from a mutual enhancement of binding-site affinity.[1-3] Clinically, co-induction may decrease toxicity and speed recovery.[2] VERSED can also abolish the excitatory effects and emergence phenomena associated with some induction agents,[5] and its potent amnestic effect may avoid breakthrough awareness at times when short-acting induction agents may be wearing off.

- **Allows lower doses of induction agents[1-5]**
- **A smooth induction[5]**
- **Less risk of breakthrough awareness[5]**
- **A smooth emergence[5]**

Dosing considerations

When VERSED is used before other intravenous agents for induction of anesthesia, the initial dose of each agent may be significantly reduced, at times to as low as 25% of the usual initial dose of the individual agents.

As a standard precaution, prior to I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and who are familiar with all dosing and administration guidelines. Reduce dosage in elderly or debilitated patients, in patients receiving narcotic premedication and in those with limited pulmonary reserve.

It is recommended that patients do not drive or operate hazardous machinery after receiving VERSED until the effects of the drug (*e.g.,* drowsiness) are gone or until the day after anesthesia, whichever is longer. The decision must be individualized.

Please see summary of product information on following page.

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FIRST

Injectable VERSED is available in 1 mg/mL and 5 mg/mL strengths.

References: **1.** Tverskoy M, et al. Midazolam-thiopental anesthetic interaction in patients. *Anesth Analg.* 1988;67:342-345. **2.** Vinik HR, Bradley EL Jr, Kissin I. Midazolam for coinduction of thiopental anesthesia in patients. *Anesthesiology.* 1990; 73(3A):A1216. **3.** Vinik HR, Bradley EL Jr, Kissin I. Midazolam-alfentanil synergism for anesthetic induction in patients. *Anesth Analg.* 1989;69:213-217. **4.** Ben-Shlomo I, et al. Midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth.* 1990;64:45-47. **5.** White PF. Comparative evaluation of intravenous agents for rapid sequence induction — thiopental, ketamine, and midazolam. *Anesthesiology.* 1982;57:279-284.

VERSED®
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INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

> Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)
>
> The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

Not intended for intrathecal or epidural administration due to the presence of the preservative benzyl alcohol.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period. Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock; coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.

Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

VERSED should only be administered IM or IV. Safety and efficacy of other routes of administration are not established.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Clearance of midazolam and certain other benzodiazepines may be delayed with concomitant administration of cimetidine (but not ranitidine). Clinical significance of this interaction is unclear.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: Excreted in human milk. Not recommended for use in nursing mothers.

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate.

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%).

IM administration to elderly and/or high-risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, patients also received other CNS depressants capable of depressing respiration, especially narcotics.

Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, bradycardia, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, hallucination, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, seizure-like activity, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site. *Hypersensitivity:* Allergic reactions, including anaphylactoid reactions, hives, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

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EDITORIAL

Pulse Oximetry: Would Further Technical Alterations Improve Patient Outcome?

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This issue of *Anesthesia & Analgesia* contains two articles that enhance our understanding of the current and future roles of pulse oximetry in clinical medicine. Young et al., cleverly utilizing rapid decompression to abruptly change alveolar oxygen tension, evaluated the speed with which several commercially available pulse oximeters are able to detect hypoxemia (1). Cullen et al. examined data, based on a change in the incidence of "unanticipated intensive care unit admissions," which suggest that pulse oximetry in fact reduces perioperative morbidity (2). Together, the two articles provide an opportunity to examine the current clinical use of pulse oximetry and to speculate about the potential of this remarkable monitoring tool to further enhance patient care. From this perspective, we will consider the clinical importance not only of the detection of hypoxemia, but also the value of its early or immediate detection. We shall also consider directions of equipment development that promise to further enhance usefulness.

The clinical importance of unexpected hypoxemia is apparent both from the remarkably high incidence in hospitalized patients and from the apparent reduction in morbidity and mortality associated with the introduction of pulse oximetry monitoring. Moller et al. (3), in a single-blind, observational study of patients undergoing general or conduction anesthesia, found that mild hypoxemia, defined as an oxygen saturation by pulse oximetry (Spo_2) of 86%–90%, developed in 53% of patients and that severe hypoxemia (Spo_2 <81%) developed in 20%. Seventy percent of the mild episodes, lasting a mean of 2.3 min, were undetected clinically; the remainder required almost 2 min for diagnosis and reversal.

Pulse oximetry, however, is applied only sporadically in other patient populations. Recent evidence confirms a high incidence of episodic hypoxemia both in critically ill patients and in patients in general care areas. In 241 patients in a surgical intensive care unit, one or more hypoxic events developed in 21%, more than half of which were detected primarily by intermittently applied pulse oximetry (4). Although most could be quickly corrected, the authors attributed two adverse outcomes to hypoxemia. More surprising is the incidence of hypoxemia in patients admitted to general care areas. In a population of patients whose primary physicians were sufficiently suspicious of hypoxemia that they requested continuous pulse oximetry monitoring, three-quarters had episodic desaturation, persisting for at least 5 min, to Spo_2 <90% and more than half to Spo_2 <85% (5). In a similar group of patients in whom clinically significant hypoxemia was *not* suspected, 32% had at least one episode of desaturation to <90% and 26% had at least one episode of desaturation to <85% (6). The relationship between these observations to morbidity, mortality, and treatment outcomes in hospitalized patients must be established.

The impact of intraoperative hypoxemia on adverse outcomes has been addressed in several important publications, most recently that of Cullen et al. in this issue of *Anesthesia & Analgesia* (2). A closed-claims analysis of 1097 anesthetic-related malpractice actions concluded that 314 incidents, nearly all of which resulted in death or brain damage, could have been prevented had pulse oximetry or pulse oximetry plus capnometry been applied (7). Eichhorn et al. (8) analyzed the incidence of severe anesthetic-related injury in the nine component hospitals of the Harvard Department of Anaesthesia before and after the introduction of monitoring standards, including pulse oximetry, in July 1985. Ten of 757,000 anesthetics administered between January 1976 and June 1985 resulted in intraoperative accidents; only one of 244,000 anesthetics given between the introduction of the standards and June 1988 resulted in accidents. This report suggested that routine monitoring could reduce anesthetic-related morbidity and mortality,

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but the extremely small numbers of severe intraoperative events precluded statistical significance.

Cooper et al. (9) took advantage of the same institutional change in monitoring standards to evaluate the impact of pulse oximetry on the incidence of more frequent, usually less severe, anesthetic events defined as "unanticipated, undesirable, possibly anesthesia-related effect(s) that required intervention, were pertinent to recovery room care, and did or could cause at least moderate morbidity." After the introduction of pulse oximetry, significantly fewer patients experienced such events, including hypotension and hypovolemia. In contrast to the study by Eichhorn et al., the experimental methodology provided a larger numerator, thereby facilitating statistical analysis; but the broader definition of "undesirable" outcomes necessarily resulted in the inclusion of a large percentage of events with a low probability of incurring actual injury or increased cost of care.

The study by Cullen et al. (2) in this issue of *Anesthesia & Analgesia* represents a logical attempt to define adverse outcomes of anesthesia such that both the number and severity of observed events are intermediate between the rare, unequivocally severe events that result in lawsuits and the frequent, often trivial, events that result in little objective evidence of injury. They chose a single sentinel event, "unanticipated intensive care unit admission," as a stronger indicator of the possibility of adverse outcome. After the introduction of pulse oximetry, the overall rate of unanticipated intensive care unit admissions decreased significantly.

The methodologic aspects of the study illustrate the formidable challenge of determining the effect of monitoring devices on patient outcomes. Death and severe neurologic injury are objective indicators that most clinicians would define similarly, but the low incidence of such events makes them impractical as statistical indicators of quality or efficacy. Hypotension, arrhythmias, and sinus tachycardia occur with much greater frequency, but are nonspecific responses to a variety of physiologic stimuli and often bear little direct relation to outcome. "Unanticipated intensive care unit admission" suggests the occurrence of an intraoperative event of sufficient severity to merit genuine concern and occurs with sufficient frequency to permit statistical comparisons between groups. However, this definition of adverse outcome does suffer from the possibility that clinicians, to the extent that they were to recognize the criterion as an indicator for quality assessment, would almost certainly reduce their enthusiasm for intensive care unit admission, thereby confounding the specificity and objectivity of the measure. The conclusions in this study are also confounded by the use of a historical control group. Other monitoring standards, particularly more widespread use of capnometry, were changed as pulse oximetry was introduced. Therefore, pulse oximetry per se may have contributed less to improved outcome than might otherwise be inferred.

Nevertheless, the weight of evidence favors the probability that the widespread application of pulse oximetry during anesthesia has been associated with fewer instances of serious morbidity and mortality. If so, would pulse oximeters that detect hypoxemia more rapidly provide additional benefit? The answer to that question necessitates one statistical and two physiologic considerations. Statistically, it seems most unlikely that faster detection of desaturation can be proven to improve outcome, regardless of how outcome is measured. An additional small decrease in an already small number would be nearly impossible to prove. The physiologic considerations include defining critical thresholds of hypoxemia and speculation upon what constitutes an acceptable delay.

Humans are surprisingly tolerant of hypoxemia under certain circumstances. Well-conditioned mountain climbers can tolerate a reduction in PaO_2 to approximately 30 mm Hg, although adaptive mechanisms produce respiratory alkalemia (10), shifting the oxyhemoglobin curve leftward, and variable, usually mild polycythemia, further increasing arterial oxygen content (11). Acute hypoxic stimuli, such as those used by Young et al. (1) and Severinghaus et al. (12,13) to test the responses of pulse oximeters to acute changes in FIO_2, are well tolerated for brief intervals even if directly measured arterial oxygen saturation (SaO_2) drops to 40% (11). If unrecognized desaturation to <81% develops in 20% of patients during anesthesia (3) and 26% of patients on general medical wards have unsuspected desaturations to <85% (6), then presumably few measurable consequences result from most episodes of transient hypoxemia. However, patients who have intercurrent diseases may be compromised by less severe hypoxemia. An increased frequency of ventricular arrhythmias may develop in unanesthetized, hypokalemic patients if SaO_2 drops below 90% (14), although ventricular arrhythmias do not increase in patients with stable chronic obstructive pulmonary disease even if saturations as low as 70%–80% develop during sleep (15). Patients with severe head injury have worse outcome if they are hypoxic on admission to the hospital (16), a clinical observation that is consistent with increased neurologic vulnerability of head-injured rats subjected to an acute reduction in SaO_2 to 75% (17). Based on the above, the empirical selection of an SpO_2 of 90% as an interventional threshold appears reasonable. The *duration* of mild to moderate hypoxemia that might be tolerated without producing harm is even more difficult to define, but again is almost certainly dependent on the presence of coexistent pathology.

Pulse oximetry should detect moderate to severe desaturation accurately and with minimal delay. However, the need to limit delay must be balanced with the need to avoid false-positive responses that will result in unnecessary intervention and potentially interfere with confidence in the monitor. Manufacturers have addressed this problem with the strategy of weighted signal averaging, such that a single sudden deviation from previous values produces little change in the displayed saturation but a sustained change or trend alters $\mathrm{Spo_2}$ (18). The delay produced by signal averaging is added to the delay produced by circulation time (approximately 10–60 s greater for finger than ear probes) (1,12) and the delay between the time that the physiologic or environmental status (i.e., $\mathrm{F{\small IO}_2}$) changes and the reflection of that change in $\mathrm{Sao_2}$. By rapidly changing atmospheric pressure, Young et al. (1) minimized the delay in environmental change. Nevertheless, that methodology does not produce as rapid a change in $\mathrm{Sao_2}$, and therefore in $\mathrm{Spo_2}$, as the approach used by Severinghaus et al. (12,13), in which a severely reduced $\mathrm{F{\small IO}_2}$ was adjusted breath-by-breath based on analysis of expired gas to produce a rapid reduction to an hypoxic alveolar plateau within 10 s. In contrast, Young et al. (1) did not consistently achieve a plateau, even within 5 min. However, the latter study did not attempt to define accuracy in relation to the criterion standard of CO-Oximetry but rather was intended to define how rapidly various pulse oximeters displayed clinically relevant changes in $\mathrm{Spo_2}$ of 5% and 10%. Viewed from this perspective, there appear to be no clinically important differences in the rate at which pulse oximeters fitted with comparable probes detect hypoxemia, although the difference between finger and ear probes is potentially important.

The technical capabilities of pulse oximeters to rapidly detect hypoxemia may have reached the limits of practical utility. Most pulse oximeters have alarms that sound each time a criterion level is exceeded. However, most clinicians recognize that the objective identification of *trends* would be as important for therapeutic intervention as knowledge of current *tests*. Even so, trends may not be readily evident because of concurrent random variation (noise), cyclical patterns, or confounding intervention effects. Implicit in the concept of *monitoring* is both the early identification of potentially adverse events in real time and the availability of repetitive measures over time ("trending"). Testing, on the other hand, measures a parameter at a fixed point in time. Much of the improved outcome attributed to pulse oximetry monitoring to date has relied on early identification, interpretation, and treatment of episodic hypoxemia in acute care settings. Little, if any, attention has been focused on the potential utility of these devices as diagnostic tools. Further improvements in trending and analysis of $\mathrm{Spo_2}$ data from pulse oximeters may enhance their utility. Improved ability to identify clinical scenarios in which episodic arterial desaturation may lead to adverse outcomes may expand the usefulness of pulse oximetry outside the acute care environment.

Analysis of serial measurements, however, constitutes a statistical problem. Measurements form a time series; that is, a collection of consecutive measures over fixed time intervals. A time series is characterized by the correlation of adjacent observations. Although statistical analysis of time series data (stochastic analysis) has a long history, mostly in the econometrics literature (19–22), little attention has been given to these phenomena in the medical literature. Nevertheless, analytical techniques used to identify trend, cyclical patterns, and intervention effects are also applicable to time series generated by medical monitors. Recent work suggests that time series may be broken down into cyclical and trend components with minimal assumptions about the form of the underlying mathematical model (23). The availability of fast computers would enable more sophisticated analysis of the monitored stochastic process so that a trend projection could be continually updated as new data points are collected. The trend projection and other pertinent information could be displayed on the monitor along with the preceding trend time series and the actual real time value.

What developments in oxygen monitoring might provide further benefit and what can pulse oximetry contribute to patient care in 1992? Pulse oximetry monitoring is frequently impossible in patients, such as those in shock, who have intense peripheral vasoconstriction. In these critically ill patients, monitoring the perfusion status of specific organs is now feasible technically and may be useful in the detection and treatment of hypoxemia in low-perfusion states. In vivo near-infrared spectroscopy, for example, continuously monitors brain oxygen saturation. This technique does not appear to be subject to deteriorating signal detection from low peripheral perfusion (24–26) and may demonstrate deterioration in tissue oxygenation before the development of significant changes in $\mathrm{Spo_2}$. This and similar monitoring devices may represent the next logical step in continuous oxygen monitoring.

Most evidence suggests that routine use of pulse oximetry intraoperatively and in the recovery room demonstrates a high incidence of otherwise unrecognized hypoxemia and, presumably, by permitting timely correction, decreases the incidence of severe anesthetic-related complications. There is little reason to expect that more rapidly responding, signal-weighting algorithms would result in any further decrease in acute morbidity and mortality in anesthetized patients. Rather, further improvements in outcome are most likely to result from extension of use outside the operating room to monitor high-risk patients (whose risk status must be carefully defined based on objective data) and from technological developments that facilitate use in patients who are not now monitored effectively. The importance and potential role of pulse oximetry as a diagnostic tool are underscored by the relatively frequent occurrence of hypoxemia outside special care areas (5,6) and their potential relationship to adverse outcomes. Indeed, of 28 patients judged to have suffered an iatrogenic cardiac arrest (out of a total of 203 arrests in hospitalized patients), three had inadequately treated, but recorded, clinical symptoms or signs of hypoxemia (27). If we assume that hypoxemia produces early clinical signs or symptoms in the minority of patients, this probably represents an underestimate. Additional studies are needed if we hope to identify, either through intermittent Spo_2 testing or the application of stochastic analysis to continuous Spo_2 monitoring, patient populations at special risk for adverse outcomes secondary to hypoxemia. Further, refinements in the monitoring of tissue oxygenation may ultimately permit the recognition and treatment of hypoxia and its attendant morbidity in patients in whom this cannot be identified adequately by pulse oximetry alone.

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Effect of Pulse Oximetry, Age, and ASA Physical Status on the Frequency of Patients Admitted Unexpectedly to a Postoperative Intensive Care Unit and the Severity of Their Anesthesia-Related Complications

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Unanticipated intensive care unit admission (UIA) associated with anesthesia served as an outcome measure to assess the quality of anesthesia care in a large teaching hospital. We characterized the patient population and types of problems associated with UIAs, attempted to identify patterns of care that could have led to specific adverse outcomes, and determined if a specific intervention, pulse oximetry, reduced UIAs. During a consecutive 65-wk period (July 1985–September 1986), 17,093 surgical patients were expected to enter the recovery room and then return to floor care. Seventy-one patients (0.42%) experienced a UIA from either the recovery room or operating room, and the circumstances of their admissions were analyzed in detail. After introduction of pulse oximetry in all anesthetizing locations (not including the recovery room) in the 29th week, the overall rate of UIAs and, specifically, the rate of UIA to rule out myocardial infarction, decreased significantly. Increasing ASA physical status (ASA-PS) and age significantly increased the probability of UIA. UIA patients with ASA-PS III/IV had a significantly higher acuity in the intensive care unit and were far more likely to die during their hospitalization than ASA-PS I/II patients. Retrospective review of UIAs alone did not identify patterns of care requiring remediation, which leads us to question the utility of UIAs as a generic screen for quality assurance.

(Anesth Analg 1992;74:181–8)

There are no standards to assess the quality of anesthesia care or the effectiveness of modifying anesthetic practice in the attempt to improve outcome. Brown (1) suggested establishing criteria of clinical performance, then monitoring specific clinical problems to ensure that these criteria were met. However, such criteria do not yet exist.

In 1987, we described a self-reporting mechanism to (a) establish a baseline rate of anesthesia-related problems encountered in the operating room (OR) and/or recovery room (RR)*; (b) assess the effect of feedback of information to the departmental staff about anesthetic complications; and (c) assess the effect of pulse oximetry on the rate and severity of complications (2). In that study, 18% of non-intensive care unit (ICU) patients admitted to a routine postoperative RR had at least one anesthesia-related event during anesthesia or in the RR that required intervention. Intensive feedback of information to the entire anesthesia department (as a group, not individually) produced no demonstrable change in the rate of recovery room impact events (RRIEs). After introduction of pulse oximetry in all ORs, the overall event rate and the rate of hypotensive and hypovolemic events were significantly reduced. The uncontrolled, longitudinal methodology precluded a conclusive demonstration of a causal relationship. We now report on the nature of the more serious events, and on how the introduction of pulse oximetry affected the frequency of unanticipated ICU admission (UIA), a relatively serious outcome, and consider the utility of UIAs for quality assurance.

Anesthesia-related, unexpected admission to an ICU, either from the RR or directly from the OR, served as an occurrence screen to focus on a specific serious outcome associated with anesthesia. This occurrence has been cited by the Joint Commission

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*At the time of this study, the term recovery room (RR) had not yet been changed to "post anesthesia care unit" (PACU). Such anesthesia-related complications were termed "recovery room impact events" (RRIEs) (2).

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on Accreditation of Healthcare Organizations as a clinical indicator of anesthesia care (3). These occurrences were stratified for age and physical status using the American Society of Anesthesiologists-Physical Status (ASA-PS) score. Our goals were to (a) assess the severity of a subset of postanesthetic complications, namely UIAs, having demonstrated previously an 18% incidence of RRIEs; (b) characterize the patient population and types of problems that were associated with UIAs; (c) identify patterns of care that could have led to specific adverse outcomes; and (d) determine if pulse oximetry was associated with a reduction in UIAs, not just a reduction in frequency of all types of complications.

Methods

This study was approved by the Hospital's Subcommittee on Human Studies.

In our earlier study, a "serious" outcome was defined as an unanticipated patient admission to an ICU (UIA or unanticipated ICU admission) after anesthesia and surgery. There were two pathways by which a patient could be admitted unexpectedly to an ICU. First, the patient could be transferred directly from the RR to the ICU. Fifty-four such patients were admitted unexpectedly to an ICU from the RR. Second, the patient could be admitted directly, though unexpectedly, to the ICU from the OR (bypassing the RR) because of surgical or anesthetic concerns that an unexpected problem required immediate intensive care. Seventeen such patients were admitted unexpectedly from the OR directly to an ICU. Patients admitted electively (per anesthetic or surgical plan) directly to an ICU were excluded (this group includes all patients having cardiac procedures or requiring postoperative monitoring with a pulmonary artery catheter and almost all patients having thoracic, vascular, and neurologic procedures). Unexpected admissions to the pediatric and neonatal ICUs were excluded. All patients who returned to floor care, by definition, did not have a UIA.

The charts of all 71 UIA patients were reviewed in detail by the senior author (D.J.C.) to characterize the problem for which unexpected ICU admission was required and the patient's hospital course. Recorded data included age, ASA-PS, ICU class (4,5), whether the event was temporary or permanent, ICU and hospital length of stay, and whether the event occurred before or after pulse oximetry was introduced in all anesthetizing locations. These recorded data were based on entries made on the medical record and were not independently validated. However, all patients admitted to the ICU from the RR or those bypassing the RR have a lengthy medical and nursing admission note placed by the ICU physicians and nurses, and in most cases, a follow-up note by the primary anesthesiologist. We determined the reason for the UIA from these specific commentaries and from our review of the anesthesia record, the surgeon's and consultant's notes, and any other miscellaneous information that contributed to our understanding of the nature of the problem. For example, it was clear when a patient was admitted to the ICU to rule out myocardial infarction (MI), as this was stated clearly in the admitting notes, the cardiology consult, the laboratory data that was obtained, and the follow-up information as the patient was ruled out for MI. Similarly, a patient who was admitted to the ICU because of unexpected intraoperative hemorrhage was easily distinguished from other categories of patients because the need for blood and volume resuscitation was clearly placed in the nursing notes, was stated in the reason for admission and the admitting notes, and was followed up by the extensive progress notes in the chart. Although the chart review was retrospective, we began with no hypothesis as to which etiologies requiring ICU admission would be affected by pulse oximetry. Only after all the data were collected did we then separate the patients into those who had UIAs before and after pulse oximetry was instituted.

During the first 28 wk of the study, only seven pulse oximeters were available for shared use in 51 ORs, primarily by the sicker patients who were most likely to be admitted electively and directly to ICUs, and thus would have bypassed the study. For the subsequent 37 wk, pulse oximeters were placed and used in essentially all patients in all 51 anesthetizing locations. Pulse oximeters were not available in the RR at that time though, on rare occasions, one could be brought from the OR if specifically requested for an airway problem.

Statistical analysis was performed using Z tests for proportions. Multivariate relationships were modeled using logistic regression analysis; age and ASA-PS were entered as graded variables, each with three equally spaced levels. For ASA-PS, we used ASA-PS I, ASA-PS II, and ASA-PS III and IV as our three levels. For age category, we used age <41, 41–65, and >65 yr as our three levels.

Results

There were 17,076 patients admitted to the RR; 17 additional patients bypassed the RR for direct but unanticipated admission to the ICU after elective surgery. Seventy-one of the 17,093 patients (0.42%) experienced a UIA and constitute the main focus of this study.

Table 1 shows the specific events that contributed

Table 1. Etiology of Specific Recovery Room Impact Events Resulting in an Unanticipated Intensive Care Unit Admission

Rule out myocardial infarction	20
Bleeding	12
Respiratory problems	
Difficulty with ventilation	11
Airway obstruction	5
Bronchospasm	4
Difficult intubation	1
Hypoxia	1
Hypotension	6
Stroke	3
Hypovolemia	3
Cardiac arrest	2
Seizure	1
Congestive heart failure	1
Hypothermia	1
Total	71

Table 2. Long-Term Results of Patients With an Unanticipated Intensive Care Unit Admission[a]

Temporary setback that prolonged full recovery	61
Permanent setback with prolonged neurologic dysfunction (one due to hypoxia)	2
Permanent setback leading to death	8

[a] $n = 71$.

Table 3. Intensive Care Unit Admission Class of Unanticipated Intensive Care Unit Admission

Class II—Intensive monitoring only	37
Class III—Intensive nursing care	32
Class IV—Intensive medical care	2

$n = 71$.

Table 4. Length of Intensive Care Unit Stay in Unanticipated Intensive Care Unit Admission Patients

	All patients $n = 71$	ASA I/II $n = 38$	ASA III/IV $n = 33$
1 Night	49	25	24
2 Nights	18	10	8
3 Nights	1	1	0
>7 Nights	3	2	1

Table 5. Postoperative Length of Hospital Stay in Unanticipated Intensive Care Unit Admission Patients

	All patients $n = 71$	ASA I/II $n = 38$	ASA III/IV $n = 33$
≤1 Week	22	10	12
1–2 Weeks	21	12	9
2–4 Weeks	17	10	7
>4 Weeks	11	6	5

to a UIA; respiratory problems ($n = 22$), postoperative bleeding ($n = 12$), and possible myocardial ischemia leading to a rule-out MI protocol ($n = 20$) (all of whom were ruled out for MI) were the most common reasons for a UIA. Sixty-one UIA patients had a temporary problem, though it may have prolonged full recovery (Table 2). One event that occurred before pulse oximetry was available led to a UIA resulting in a permanent deficit with prolonged but minimal brain damage (6). The eight deaths resulted from surgical complications and/or the natural course of the patient's disease, not from the anesthesia-related event.

Having categorized these 71 UIA patients by an ICU classification system about which a great deal is known (4,5) (Table 3), most of these UIA patients were not critically ill. Thirty-seven of the 71 UIA patients were class II, i.e., primarily in the ICU for observation and monitoring, rather than for active therapy. Thirty-two patients were class III, requiring intensive nursing care despite a stable medical condition, and were discharged from the ICU within 1 or 2 days. Only two patients were class IV on admission to the ICU. One of these patients suffered the inevitable result of his disease process, and one patient had anesthetic-related hypoxic brain damage. As expected from the low level of critical illness demonstrated by this patient cohort, most patients (49/71) spent only one night in the ICU (Table 4). Sixty-one UIA patients were discharged from hospital within 1 mo (Table 5). Median hospital length of stay was 12 days.

Both ASA-PS and age were associated with the frequency of UIAs, which increased from 0.05% in ASA-PS I patients to 1.48% in ASA-PS III/IV patients (Figure 1). Similarly, the incidence of UIA was significantly higher in patients older than 65 yr of age (1.02%) than in those less than 41 yr of age (0.06%) (Figure 1). Both increasing age ($P = 0.0047$) and ASA-PS ($P = 0.0002$) independently related to an increased incidence of UIAs (logistic regression analysis). For each one-step increase in age category, holding ASA-PS constant, the probability of a UIA increased by a factor of 1.82 (95% CI = 1.54–3.38). For each one-step increase in ASA-PS, holding age category constant, the probability of a UIA increased by a factor of 2.33 (95% CI = 2.18–5.12). Fifty-six of 71 (79%) patients with a UIA were either more than 65 yr of age or had ASA-PS III/IV, or both, although overall only 5543 of 17,093 (32%) patients were more than

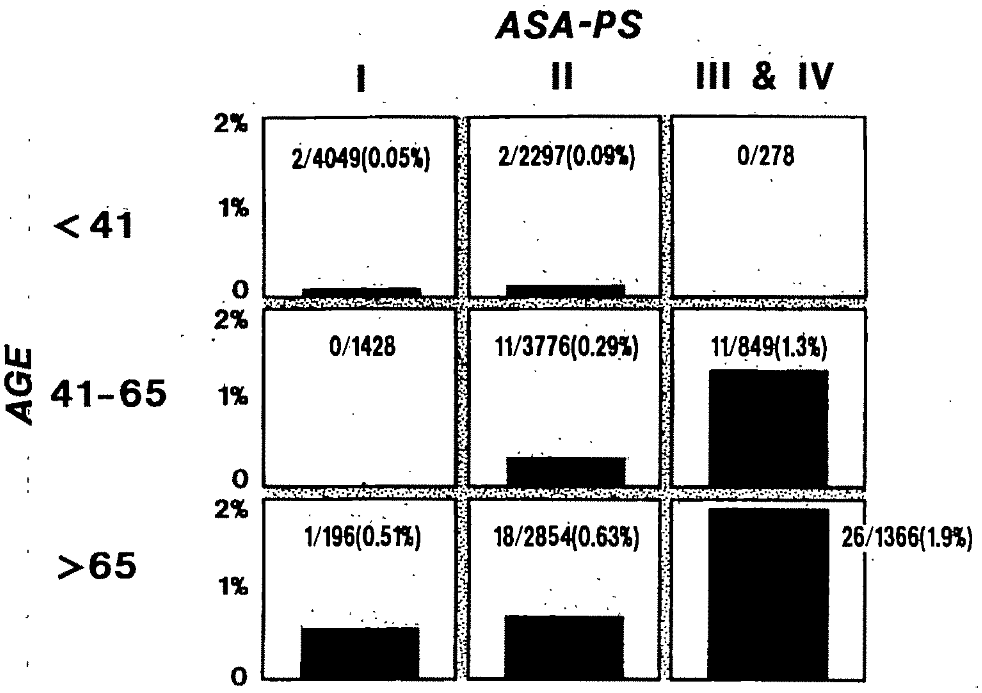

Figure 1. The frequency of a "serious outcome" (unanticipated intensive care unit admission) is shown as a function of increasing American Society of Anesthesiologists Physical Status and age. The percent of patients with a "serious outcome" increased significantly as age ($P = 0.0047$) and ASA-PS ($P = 0.00002$) increased (logistic regression).

Table 6. Effect of American Society of Anesthesiologists Physical Status on Outcome Measures

	ASA I/II	ASA III/IV	Z	*P*
All patients (*n*)	14,600	2,493		
UIA (*n*)	38	33		
Rate/10,000	26	132	7.06	<0.0001
Bleeding (*n*)	7	5		
Rate/10,000	4.8	20.1	2.65	0.004
Rule-out-MI (*n*)	12	8		
Rate/10,000	8.2	32.1	3.22	0.0006
Became ICU class 3 (*n*)	17	20		
Rate/10,000	11.6	80.2	6.8	<0.0001
Died during hospitalization (*n*)	2	7		
Rate/10,000	1.4	28.1	5.34	<0.0001

UIA, unanticipated intensive care unit admission; MI, myocardial infarction; ICU, intensive care unit.

65 yr and/or ASA-PS III/IV ($P < 0.0001$). Of the 17,093 patients anticipating admission to the routine RR after anesthesia and surgery, approximately six times as many were ASA-PS I/II ($n = 14{,}600$) as were ASA-PS III/IV ($n = 2493$) (Table 6). Yet, nearly half of the UIAs occurred in ASA III/IV patients (33/71, $P < 0.0001$). More ASA-PS III/IV patients per 10,000 were UIAs for bleeding ($P = 0.004$) or to rule out an MI ($P = 0.0006$). ASA-PS III/IV patients who experienced a UIA were seven times more likely to become ICU class 3 patients than were ASA I/II patients ($P < 0.0001$). ASA-PS III/IV patients who required unexpected ICU admission were 20 times more likely to die during their hospitalization than ASA I/II patients who had a UIA ($P < 0.0001$). There were no significant differences between ICU length of stay and postoperative hospital length of stay comparing ASA-PS III/IV patients and ASA-PS I/II patients who had UIAs (Tables 4 and 5).

Monitoring all patients with pulse oximetry was associated with a significantly lower rate of UIAs, just as it was associated with a lower frequency of all RRIEs in the previous study (2) (Figure 2) (Table 7). Forty-six UIAs occurred in 7181 patients during the 28 wk before pulse oximetry was introduced (64 per 10,000 patients), whereas 25 UIAs occurred in 9912 patients during the 37 wk after pulse oximetry was introduced (25 per 10,000 patients) ($Z = 3.9$, $P < 0.0001$).

In the 28 wk before pulse oximetry, the UIA rate to rule out MI was 19 per 10,000 patients; in the 37 wk after the introduction of pulse oximetry, the rate was 6 per 10,000 patients ($P = 0.0037$). There were no significant differences preoximetry to postoximetry in patients with UIAs from bleeding or ventilation problems, but with the small number of cases, the confidence intervals are wide and a substantial decrease could exist but fail to be demonstrated by this study. [Bleeding problems: change = −4.7 ± 8.6 cases per 10,000. Ventilations problems: change = −9 ± 11.7

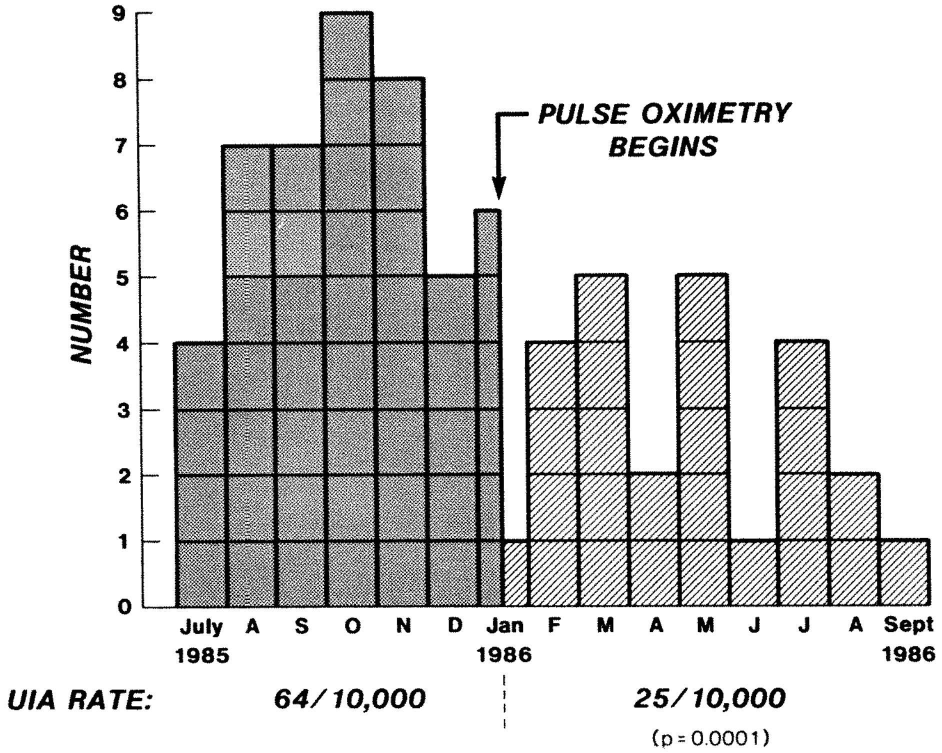

Figure 2. The number of UIAs per month is depicted before and after the introduction of pulse oximetry. The number of UIAs decreased significantly after pulse oximetry was introduced.

Table 7. Effect of Pulse Oximetry on Outcome Measures

	Preoximetry (*n*)	Postoximetry (*n*)	Z	*P*
All patients	7,181	9,912		
UIA	46	25		
Rate/10,000	64.1	25.2	3.9	<0.0001
Rule-out-MI	14	6		
Rate/10,000	19.5	6.05	2.68	0.0037
Bleeding problems	7	5		
Rate/10,000	9.73	5.04	1.15	0.1251
Ventilatory problems	13	9		
Rate/10,000	18.1	9.1	1.62	0.0526
Other	12	5	2.38	0.0089
Rate/10,000	16.7	5.04		
ICU class 3	19	13		
Rate/10,000	26.5	13.1	1.815	0.0351
Died during hospitalization	5	4		
Rate/10,000	7	4	0.83	0.2033

UIA, unanticipated intensive care unit admission; MI, myocardial infarction; ICU, intensive care unit.

cases per 10,000.] There were also no differences in the distribution of patients by ASA-PS or age category in the preoximetry to postoximetry period. Although significantly more UIA patients became ICU class 3 before oximetry, there was no difference in hospital mortality rate preoximetry to postoximetry.

Discussion

Of the 17,093 patients expected to enter the routine RR after anesthesia and surgery, 71 (0.42%) suffered a UIA, including one previously healthy patient who suffered a small degree of permanent neurologic impairment as a result of an hypoxic event.

Patients *electively* admitted to an ICU were *not* included in this study. Most such patients have little physiologic reserve, so it is difficult to determine which events are "expected" versus "unexpected" during a major surgical and anesthetic intervention. By reviewing all direct admissions to our two noncardiac surgical ICUs from the OR during this study, we strongly believe that no UIA patients were missed.

It is intriguing to compare our results with those at a single, tertiary care hospital in Canada (7,8). Their overall morbidity was 17.5% of patients who suffered some form of anesthetic complication, most of which were minor. This is very similar to our RRIE rate of 18% (2). Cohen and Duncan defined major complications as events that were life threatening, that prolonged hospitalization, or that left lasting morbidity. Their rate of major complications was 0.45%, similar to our UIA rate of 0.42%. Although our definition of a UIA differs from their definition of a major complication, both attempt to define an intermediate outcome, something less than death or severe permanent brain damage. Thus, our results and theirs represent a similar magnitude of effect.

As was first shown by Cohen and Duncan (9), the frequency of anesthetic complications increased with ASA-PS. Keats (10) has called for stratifying populations and grading outcomes of anesthesia, and both of these techniques were incorporated in this study. Stratifying by age and ASA-PS demonstrated that most elderly ASA-PS III/IV patients are unlikely to have a UIA (less than 2% of those patients older than 65 yr and ASA III/IV suffered a UIA). However, when a UIA does occur, the elderly and ASA-PS III/IV patients are those most likely to be affected (Figure 1). The increased probability of UIA with increasing age and/or ASA-PS indicates the importance of these two variables in the frequency of UIAs. However, we could not identify a pattern that would predict which of the older, sicker patients would be admitted to the ICU. Perhaps studies at institutions that concentrate more on this population could demonstrate patterns that lead to UIA. As most of the UIAs were temporary, yielded a low level of critical illness compared to our usual ICU population, and required a short stay in the ICU, we believe the severity of anesthesia-related complications in the context of a large, acute general hospital is acceptably low. From the patient's or family's perspective, one or two nights in an ICU being weaned from mechanical ventilation or being monitored to rule out an MI may be a frightening experience. However, to intensivists dealing with a wide spectrum of critically ill patients, the vast majority of these UIA patients represented the least critically ill among an ICU patient population. The marginal cost of additional ICU time adds to the overall cost of care, but was not addressed specifically in our study.

In our previous study, we noted that there was "only weak evidence to support the conclusion that pulse oximetry was related to a lower rate of hypotensive and hypovolemic events" (2). This detailed review of a more serious outcome (UIA) strengthens the association between pulse oximetry and improvement in outcome, but does not prove a causal connection. Fewer patients were unexpectedly admitted to the ICU after pulse oximetry was initiated. There was no change in admitting policy during the time of the study; the clinical definitions or thresholds for admitting patients to an ICU did not change; and we see no reason why chart review would miss unanticipated admissions to the ICUs, as admission to the ICU is an explicitly defined outcome. We are not aware of any change in the surgical patient population, anesthetic management, number of house officers and their supervision, or quality of the surgical or anesthetic staff during the 65 wk of this study. As residents enter and leave our program on a staggered basis, we determined the overall months of experience of our house staff before or after pulse oximetry was introduced and found no difference (Figure 3). Anesthesia staff turnover as well as leadership was stable as it has been before and since the study. Thus, we cannot account for external variables that might have changed preoximetry to postoximetry.

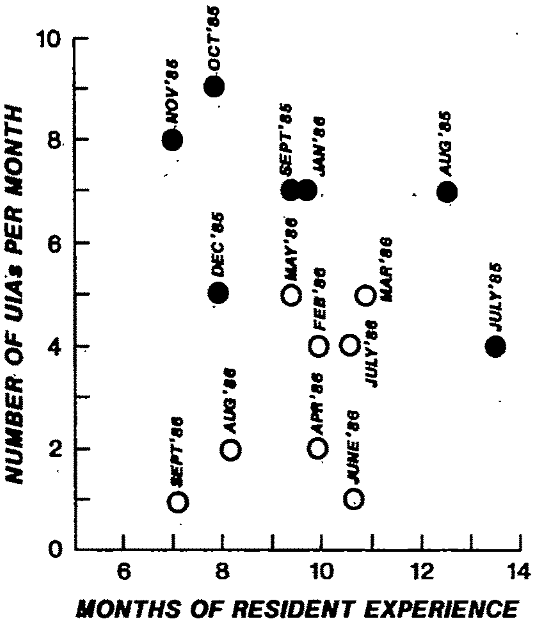

Figure 3. The number of UIAs per given month is shown as a function of the average months of experience of our house staff, before and after pulse oximetry was introduced. There is no relationship between the average monthly house-staff experience and number of UIAs preoximetry or postoximetry. ●, July 1985–January 1986 (preoximetry); ○, February 1986–September 1986 (postoximetry).

What, then, can explain the decreased rate of UIAs? Those etiologies leading to a UIA that are not expected to change use of pulse oximetry, e.g., intraoperative or postoperative hemorrhage, were unaffected by the introduction of pulse oximeters in all ORs. However, the rate of rule-out-MI did decrease significantly after introduction of pulse oximetry. Use of pulse oximetry probably identifies many hypoxemic, hypotensive, or low-perfusion states before subsequent ischemic changes occur, are recognized, or persist long enough to cause major concern. Either decreasing oxygen saturation or loss of signal should stimulate the anesthesiologist to intervene, perhaps preventing the kind of electrocardiographic events that typically result in an order for a rule-out-MI protocol.

Moller et al. (11) have also recently shown that myocardial ischemia, defined by angina or ST segment depression, occurred in significantly fewer patients monitored by pulse oximetry than in a control group who were not monitored with pulse oximetry.

They, too, suggest an association between pulse oximetry, hypoxemia, and myocardial ischemia.

Unanticipated ICU admissions, used as an anesthesia outcome measure from the OR or RR to an ICU, has not been studied to determine its efficacy in identifying problems amenable to correction. However, Sanazaro and Mills (12) assessed generic screening including the unplanned transfer to the ICU, though it appeared that these unplanned transfers were from acute care wards, not from the RR or the OR directly. They noted the following: (a) The effectiveness of generic screening and quality assessment largely depends on the validity of peer review, which has been seriously questioned by numerous authors. (b) Generic screening lacks any inherent relationship to the quality of patient care. The number of patients transferred to ICUs has no *direct* implications for quality. Only after the reasons for transfer are known and analyzed can the findings be used to assess quality. Our attempts to examine the reasons for transfer did not yield useful trends in assessing quality of care. (c) Generic screening does not produce the type and quantity of data needed to decide whether the overall performance of individual staff members warrants continuing their clinical privileges. It can only identify the rare practitioner who has a readily observable series of serious complications. As our study was anonymous, we did not attempt to identify any practitioners, and thus could not evaluate a series of serious complications applicable to one practitioner. We expected that review of UIAs, an explicit outcome measure, would yield more information relevant to clinical practice than the review of all RRIEs because extraordinary measures are used when caring for patients unexpectedly admitted to an ICU, higher costs are incurred, and the impact on patients, families, and clinical personnel is much greater compared with RRIEs, 99.58% of whom recovered with routine clinical management. Using UIAs as an outcome measure to test the effect of one intervention, pulse oximetry, we did not identify any specific problems, patterns, or indications of deficiencies in patient care that require remediation. Ironically, a single event, the hypoxia case mentioned earlier, had far more departmental impact than reporting UIAs. That patient was not monitored with pulse oximetry because pulse oximetry was unavailable routinely at the time. That incident led the department to immediately purchase pulse oximeters for all ORs, a decision that was implemented in toto at the 29th week of our study. Perhaps more intensive, *immediate* investigation using information not typically documented in the medical record (e.g., interviews) would have identified problems requiring and amenable to remediation.

The feasibility and acceptability of prospectively identifying specific complications by using existing review mechanisms, for example, concurrent utilization review, has been demonstrated in many hospitals. Prompt identification of all complications has three major advantages. First, the data are more complete than those found in records; second, timely data collection permits prompt peer review of all serious complications and intervention and care if indicated; third, identifying specific outcomes as they occur facilitates accurate compilation of numerator data for calculating the incidence of each complication (12).

This study has established the incidence of UIAs in a large teaching hospital. As no standard exists to examine anesthesia morbidity as a measure of outcome, these data represent only a first step in quantifying anesthesia-related quality of care. Because each hospital's practice pattern differs in a number of ways—e.g., surgical disease, definitions of complications and outcome, patient mix and acuity, use of invasive procedures, skill level of medical and nursing personnel and whether all patients are admitted to a RR or some bypass the RR to an ICU—UIA rates will not be directly comparable. Anesthetic complications are already extremely low in terms of long-term sequelae and serious outcome (13). Efforts to identify and reduce still further the occurrence of the rare but disastrous complications are still needed.

In summary, we have (a) reported a rate of UIAs, (b) shown that pulse oximetry was associated with a lower overall rate of UIAs and, specifically rule-out-MIs in our institution, (c) identified the magnitude of additional risk for UIA as ASA-PS and age increased, and (d) *questioned* the usefulness of UIA as a generic screen.

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Response Time of Pulse Oximeters Assessed Using Acute Decompression

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In human volunteers, the response times of 11 pulse oximeters to a 10% step reduction in arterial oxygen saturation were measured using an acute decompression technique. When finger probes were used, nine oximeters had similar response times and two were significantly slower ($P < 0.05$). The ear probe response time was similar on six oximeters assessed, and faster than the finger probes. The response times of the oximeters to an acute increase in arterial saturation were tested by suddenly changing the inspired gas from air to 100% oxygen at an ambient pressure of 380 mm Hg. For ear probes, the response times were similar for all oximeters; for finger probes, three fast-responding and three slow-responding oximeters were identified ($P < 0.05$). A faster response could be elicited by placing the probes on the thumb ($P < 0.05$). We conclude that if a rapid indication of changes in arterial saturation is required, pulse oximeters with ear probes should be used. If finger probes are used, they should be placed on the thumb. The oximeter used will influence the response time if finger probes are used, but it will have little effect if ear probes are used.

(Anesth Analg 1992;74:189–95)

Pulse oximeters have transformed practice in anesthesia and intensive care by providing a continuous indication of arterial oxygen saturation. Several studies have suggested that there may be a significant delay between changes in alveolar oxygen tension and a change in the oximeter reading (1–3). If alveolar oxygen tension is decreasing rapidly, actual arterial saturation might decrease to low values before any warning is given by the oximeter. In a theoretical study using the MacPuf computer model of the cardiorespiratory system, Verhoeff and Sykes (4) found that a delay of 1 min between a change in alveolar oxygen tension and an indication on the oximeter could potentially result in damaging hypoxia.

To measure the response time of an oximeter, the arterial saturation must be changed as rapidly as possible: the ideal is an instantaneous step from one saturation to another. Severinghaus et al. (1,2) produced rapid changes in arterial saturation by asking volunteers to hyperventilate voluntarily while breathing hypoxic gas mixtures. The inspired gas mixture was adjusted breath-by-breath to achieve the fastest possible decrease in alveolar oxygen tension and hence arterial saturation. Using this method, the rate of decrease of alveolar oxygen tension and hence arterial saturation depends not only on the inspired oxygen tension but also on the alveolar ventilation and functional residual capacity, which may differ between subjects. However, if the ambient pressure is rapidly reduced, the partial pressure of oxygen in the alveoli will also decrease in proportion, simultaneously producing a decrease in alveolar oxygen tension independent of either functional residual capacity or alveolar ventilation. This step decrease in barometric pressure can be achieved by decompression of a hypobaric chamber.

The total response time of an oximeter to a step change in alveolar oxygen tension has two components. First, the blood has a transit time from the lungs to the probe site, and second the oximeter takes a period of time to sense and display a change in saturation. This latter delay, which we have termed the machine response time, depends on the design of the oximeter and the algorithms used for filtering and

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artifact rejection in the oximeter software. If several oximeters are placed on the fingers of the same subject and the arterial saturation is then changed abruptly, a measure of the machine response times relative to one another can be obtained if the circulation time to all the oximeter probes is assumed to be the same. Because the circulation time is difficult to determine, mathematical evaluation of the actual machine response time cannot be performed. However, comparison of the individual total (machine + circulation) response times to the averaged total response time for multiple oximeters on one subject gives a useful method of ranking oximeter response times. The mean total response time for all the oximeters consists of the circulation time added to the mean of all the machine response times. By subtracting the mean total response time for one subject from the response time of any individual machine, the circulation time is cancelled out. This leaves a value indicating how much faster or slower any oximeter machine response time is compared with the mean machine response time for all the oximeters.

Methods

Thirteen oximeters from 10 manufacturers were studied, with a total of 21 different probes. The oximeters were either loaned by the manufacturers or were in clinical use at our institution. Details of the machines are listed in Table 1. We had one model from each manufacturer except Kontron who supplied us with three identical oximeters to allow simultaneous comparisons of their probes and Ohmeda who supplied two models to test. All oximeters were operated according to the manufacturer's instructions. If the averaging time could be varied, it was set to the shortest time period. An analogue output was standard for all oximeters except the Novametrix, to which an analogue output adaptor module was added.

Table 1. Machine Data

Oximeter	Probes used	Number of tests	On loan?	Averaging time
Kontron 7840 (3 machines)	Neonatal	10	Yes	4 beats
	Pediatric	11		
	Adult	10		
	Reflectance[a]	11		
	Ear	9		
Minolta Pulsox-7	Finger	12	Yes	Not stated
	Ear	6		
Physiocontrol Lifestat 1600	Finger	11	Yes	Not stated
	Ear	8		
Critikon Oxyshuttle	Finger	15	Yes	Beat-to-beat
	Ear	2[b]		
Novametrix type 515	Finger	17	Yes	2 s
Datex Satlite	Finger	16	No	Not stated
Datascope Accusat	Finger	11	Yes	Not stated
	Ear	8		
Nonin 8604	Finger	14	Yes	Not stated
Ohmeda 3700	Finger	11	Yes	3 s
	Ear	7		
Ohmeda 3740	Finger	11	No	3 s
Nelcor N200[c]	Finger	13	No	2–3 s

[a] Prototype finger transmittance/reflectance probe supplied by Kontron.
[b] Only two runs with ear probe owing to error in randomization.
[c] Used without electrocardiographic synchronization (C-lock).

The study was performed in a hypobaric facility at the Royal Air Force Institute of Aviation Medicine. This chamber is normally used for studies in altitude physiology and the assessment of life support equipment. It comprises a test chamber containing the subjects, connected via a valve to a reservoir chamber. The reservoir chamber is evacuated to a preset subatmospheric pressure. When the valve between the chambers is opened, the pressure in the test chamber rapidly decreases. For these experiments the test chamber was initially slowly evacuated to a pressure of 565 mm Hg (74.3 kPa) absolute (equivalent to 8000 ft altitude), corresponding to an inspired oxygen partial pressure of 108 mm Hg (14.2 kPa). The subjects were then decompressed over 3 s to an ambient pressure of 380 mm Hg absolute (50 kPa or 18,000 ft). After decompression, the inspired oxygen partial pressure was 69 mm Hg (9.1 kPa) and might be expected to produce a decrease in arterial saturation from 93% to 72% (5).

Eleven nonsmoking, healthy men aged 18–43 yr were studied. They were recruited from the staff of the Institute and Royal Air Force personnel. All subjects had previous experience of decompression. They had no history of hemoglobinopathies. Twenty decompressions were performed, so nine subjects were studied twice. No subject was decompressed more than once on the same day. Each subject in turn was seated in the chamber, with his hands resting on the arms of the chair. A continuous noninvasive blood pressure monitoring system (Finapres, Ohmeda) was used throughout with the cuff attached to the index finger of the right hand.

An aircrew helmet and mask were fitted, with the inlet hose of the mask open to ambient chamber air. The mask provided support for the gas sampling probe that was passed through a port in the mask to a point in front of the lips. This was connected to a respiratory mass spectrometer (Centronics 007) to monitor inspired and end-tidal oxygen and carbon dioxide tensions. A communication system fitted in the mask and helmet allowed the subject to communicate with the experimenters outside the chamber.

Each subject was fitted with 11 oximeter probes, one on each finger (except the right index finger) and one on each ear. The probe and site combinations were randomized. The hands were covered to exclude ambient light and the helmet covered the ear probes. The leads from the probes, the noninvasive blood pressure monitor, and the sampling probe for the mass spectrometer passed through a seal in the chamber wall to the instruments that were positioned outside the chamber.

The analogue outputs from the oximeters passed to three 8-channel pen recorders. Each recorder also recorded a synchronizing signal, and a chamber pressure signal. The electrocardiogram, arterial blood pressure, and oxygen and carbon dioxide tension at the lips were also recorded. The mass spectrometer was calibrated against gas standards at a pressure of 380 mm Hg to avoid any nonlinearity in response owing to changing pressure at the sampling probe. The oximeter channels were calibrated using a voltage standard according to the oximeter manufacturer's specifications, except for the Nonin which generated its own calibration voltages.

After the apparatus had been checked and calibrated, the chamber was sealed and slowly decompressed to 565 mm Hg. When all the oximeter readings had stabilized, the subject was decompressed to 380 mm Hg over 3 s. The decrease in pressure was exponential, so most of the change occurred within the first 2 s. This pressure was maintained for 5 min with the subject breathing air. An aircraft oxygen system delivering 100% oxygen was then connected to the mask hose, and the subject was instructed to hyperventilate. When the readings on the oximeter were stable (usually 30–40 s later), the experiment was terminated and the chamber was slowly recompressed to atmospheric pressure.

For all the decompressions, a safety officer (breathing oxygen-enriched air) was present with the subject in the chamber. The study was approved by the Ethics Committee of the Institute of Aviation Medicine, and all subjects gave written informed consent.

For each decompression run, a baseline reading at 565 mm Hg ambient pressure for each of the nine oximeters with finger probes was recorded from the paper chart. The baseline reading was taken as the mean saturation value for 5 s before decompression. The time taken for the saturation reading to decrease by 10% from the baseline was then recorded for each of the nine oximeters. Statistical analysis was performed on the total response times using an unbalanced analysis of variance that assumed three additive effects: the decompression run, the oximeter, and the finger used. The response times were logarithmically transformed before analysis to ensure normality of the residual values.

The response times for each decompression run were averaged to give the mean times for all nine oximeter readings to decrease by 10%. The mean times were subtracted from the individual oximeter response times. This gave the difference in response time for each of the nine oximeters from the mean response time for that decompression run (relative response time), which is a measure of the machine response times of the oximeters independent of the circulation time. The relative response times for each use of the same oximeter/probe combination were averaged for all the decompression runs to give the final result.

To compare two machines, their relative response times can be subtracted (noting sign) and the result interpreted as "on average oximeter X will show a 10% decrease in saturation Y seconds faster (or slower) than oximeter Z." The statistical significance of this result is determined by the analysis of variance.

To test the response to a stepwise increase in saturation caused by a sudden increase in inhaled oxygen tension, a similar analysis was performed except the analysis of variance was undertaken without logarithmic transformation of the results. The baseline for each oximeter was the mean reading for 5 s before the first breath of oxygen (as determined by an increase in the inspired oxygen tension measured by the mass spectrometer).

Ear probes were available for six of the oximeters. Only two ear probe/oximeter combinations were studied for each decompression. The analysis described above for removing the effect of circulation time for finger probes was not appropriate in this circumstance, so the mean total (decompression to a 10% decrease in saturation) response times were calculated for all the uses of each ear probe/oximeter combination. An analysis of variance was used to separate the effects of probe site (left or right ear), oximeter, and decompression run after logarithmic conversion of the data. A *t*-test was used to determine if the total response time was significantly different using the same oximeter with ear and finger probes.

A value for arterial saturation was calculated from the end-tidal oxygen and carbon dioxide tensions using the formula described by Severinghaus and Naifeh (1). This assumes that the subject is at 37°C and has normal values for acid-base status, hemoglobin oxygen affinity, and alveolar-to-arterial oxygen tension gradient. This value was calculated breath-by-breath for the whole decompression period.

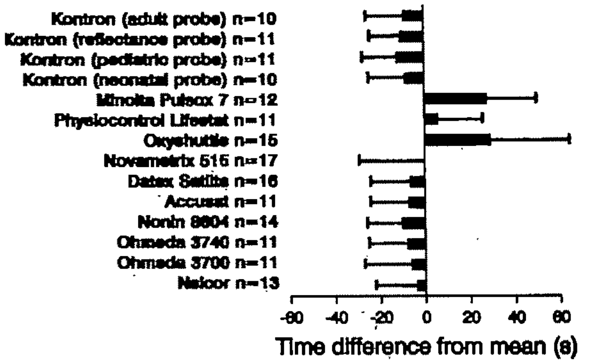

Figure 1. The relative time taken to show a 10% decrease in saturation after acute decompression. The oximeters were fitted with finger probes. The response times are the mean relative response times, as explained in the text. The error bars indicate one standard deviation.

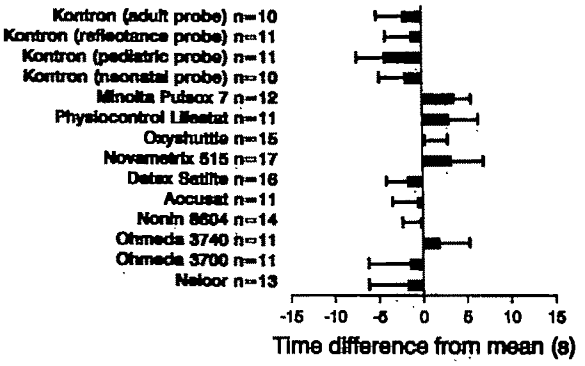

Figure 2. The relative time taken to show a 10% increase in saturation after a sudden change from air to 100% oxygen as the inspired gas at 380 mm Hg ambient pressure. The oximeters were fitted with finger probes. The response times are the mean relative response times, as explained in the text. The error bars indicate one standard deviation.

Results

For a 10% decrease in saturation using finger probes, the Oxyshuttle and Minolta machines had a significantly slower response time than all the other oximeters except the Physiocontrol, using a significance level of $P < 0.05$. The response time of the Physiocontrol was not significantly different from any other oximeter. There was no significant difference between the finger used or between the different probes on the Kontron machines. The relative response times are shown in Figure 1. The mean delay between the fastest (Kontron with a pediatric finger probe) and the slowest (Oxyshuttle) was 38 s. Total (circulation + machine) response times ranged from 17 to 150 s.

For a 10% increase in saturation, the Physiocontrol, Minolta, and Novametrix oximeters were significantly ($P < 0.05$) slower than the Kontron and Datex oximeters. The Minolta oximeter was also significantly slower than the Nelcor and Ohmeda 3700 oximeters. No other comparisons between oximeters were statistically significant. The probe placed on the thumb had a significantly faster response time than that placed on the other digits. The relative response times are shown in Figure 2.

The mean total response time for the ear probes (the time between the beginning of decompression and a 10% decrease in the saturation reading) are shown in Figure 3. Only six oximeters with ear probes were available for testing. The Oxyshuttle probe was only tested twice, so no error bars are shown on the diagrams for this machine. The difference in total response time between the mean values of the fastest and slowest oximeters for a 10% decrease in saturation was 61.5 s. The Accusat and Minolta oximeters were significantly faster when used with ear probes compared with finger probes ($P < 0.02$).

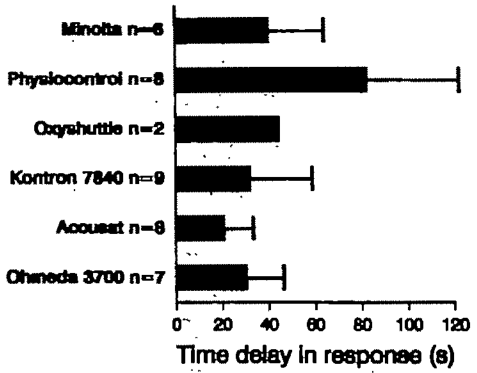

Figure 3. The total time taken for oximeters fitted with ear probes to indicate a 10% decrease in saturation after acute decompression. The error bars indicate one standard deviation. Only two determinations were made using the Oxyshuttle, so no error bar is shown.

The total response times for a 10% increase in saturation using ear probes are shown in Figure 4. For both an increase and decrease in saturation, there was no statistically significant difference between oximeters or between the ear used.

The means of all saturation readings for all subjects for ear and finger probes for the whole experiment are shown in Figure 5. The mean saturation calculated from the end-tidal gas tensions from all runs is also shown. For both the decrease and increase in saturation, the ear probe response precedes the finger probe response but both are nearly parallel. As the decompression period proceeds, the mean measured saturation decreases more rapidly than the calculated saturation, and hence the two values diverge.

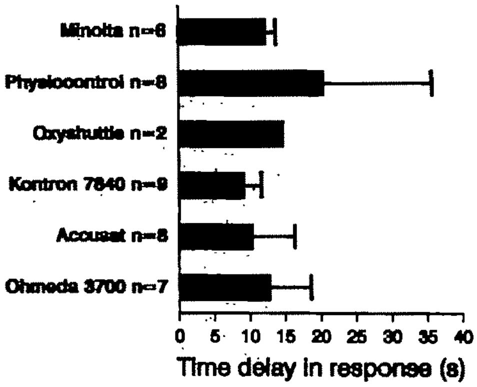

Figure 4. The total time taken for oximeters fitted with ear probes to indicate a 10% increase in saturation after a sudden change in inspired gas from air to 100% oxygen at 380 mm Hg ambient pressure. The error bars indicate one standard deviation.

Discussion

Rapid changes in alveolar oxygen tensions can be achieved either by acute decompression or by breathing hypoxic gas mixtures. There are theoretical advantages to using acute decompression rather than hypoxic gas mixtures to produce a step change in arterial saturation. The change in alveolar oxygen tension, and hence arterial oxygen tension and saturation, is independent of respiratory rate, alveolar ventilation, and functional residual capacity and can be predicted from the change in chamber pressure. However, the safe limits for pressure changes during decompression restrict the magnitude of the step change in alveolar oxygen tension. The initial decompression to 565 mm Hg used in these experiments ensured the initial arterial oxygen tension was close to the steep portion of the oxyhemoglobin dissociation curve, and any further reduction in arterial oxygen tension would cause a large change in saturation. Using this technique, the arterial saturation calculated from end-tidal gas tensions decreased from an average of 97% to 87% in the time between decompression and the first breath after decompression (approximately 3 s). A larger step change in saturation would have required an unacceptably large pressure change during decompression. This 10% change contrasts with the 21% change that we predicted from published data (5), although the measured saturation finally decreased to an average of 76%. We believe this is caused in part by the mixed venous blood returning to the lungs with an oxygen partial pressure as high or higher than the alveolar oxygen tension during and after decompression. Thus during acute decompression, the alveolar oxygen tension will rapidly decrease to a level close to the mixed venous tension. The alveolar oxygen tension will then be buffered by the mixed venous blood. The alveolar oxygen tension, and hence arterial saturation, will then decrease at a slower rate, depending on alveolar ventilation, cardiac output, oxygen consumption, and blood oxygen carrying capacity. There is an obvious biphasic response of saturation to acute decompression (Figure 5). The initial rapid decrease in saturation is followed by a slower, nearly linear decrease over the course of the experiment. The values quoted for arterial oxygen saturation at various altitudes (5) are measured at equilibration and hence are closer to the values found at 3 min than those found just after acute decompression.

Severinghaus et al. (1,2) attempted to produce a rapid decrease in alveolar oxygen tension by hyperventilating their subjects with hypoxic gas mixtures. The initial inspired oxygen tension was very low, and they added more oxygen as the experiment progressed to produce a hypoxic plateau. The resulting 40%–50% decrease in (calculated) saturation took about 12 s. Thus the decompression technique provides a very fast 10% decrease in saturation but is limited by safety considerations and the buffering effect of the mixed venous blood. The hypoxic mixture technique is subject-dependent but can be used to produce larger acute decreases in saturation.

It is not possible to test the response times of oximeters to a step increase in saturation by using rapid increases in ambient pressure in the chamber used in these experiments. We therefore asked the subjects to breathe 100% oxygen to cause a rapid increase in arterial saturation. The calculated saturation was greater than 97% in all subjects after the first breath of oxygen. The oxygen tension of the mixed venous blood has no effect in this circumstance.

By comparing each oximeter response time with the mean response time for each subject, the effects of the circulation time are removed. However, although this gives a set of values for the individual machine response times relative to the mean machine response time for that subject, it is not possible to calculate an absolute value for machine response time without a measure of the circulation time. We found a wide range of total response times (circulation + machine response times), indicating that there is probably a wide range of lung-finger circulation times in our subjects. The averaging method we used to remove the influence of circulation time would be most effective if the same oximeter probe combinations were tested on all subjects. In this situation, the mean machine response time would be expected to be the same for all subjects. We attempted to study a wide range of oximeter/probe combinations, and so the oximeters used on different subjects varied. The mean machine response time would thus be expected to vary between runs. This will increase the variability of the results: if one run was performed using

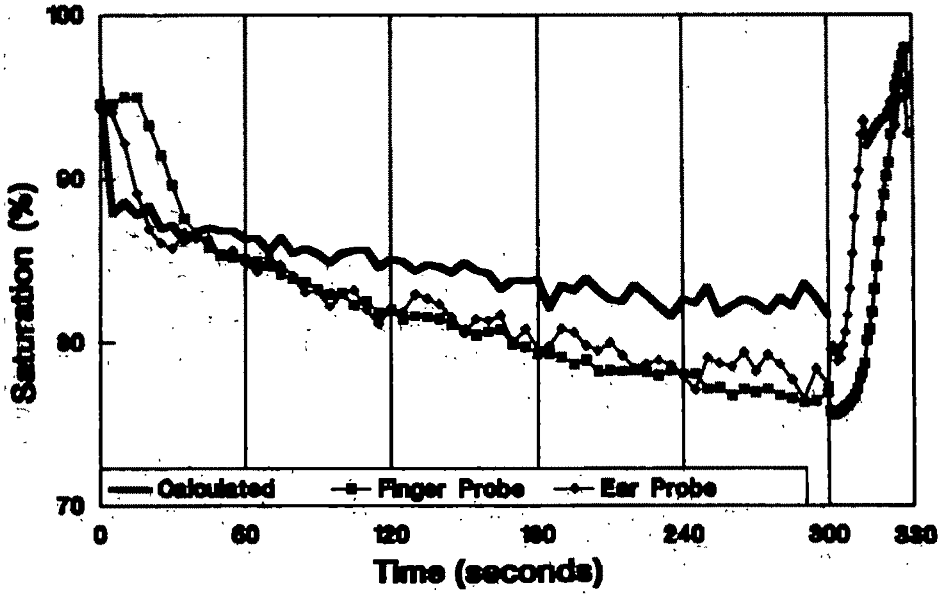

Figure 5. The mean saturation for all 20 decompressions and all oximeters plotted against time. Acute decompression occurred at 0 s, and the subjects switched from air to 100% oxygen as the inspired gas at 300 s. The saturation calculated from the end-tidal gas tensions is also shown. Each point for the calculated saturation is the mean of 20 determinations for the first 180 s and 19 for the remainder (the first subject was only decompressed for 3 min). Each point on the finger probe plot represents the mean of 179 for the first 180 s and 168 points for the remainder. The ear probe data are the mean of 40 and 38 determinations. Standard deviations are not shown for clarity. There are no values for calculated saturation after the subjects started to breath supplemental oxygen (300 s) as the expired oxygen tension values exceeded the chart recorder scale.

predominantly slow oximeters, for example, the mean machine response time would be quite long and the difference between the mean machine response times and the response times for the slow oximeters would be small. We tried to minimize these factors, while testing a large number of oximeters, by using 20 decompressions. We believe that this effect may explain much of the variability in the results.

The response time of an oximeter to a *decrease* in arterial saturation is clinically more important than the response to an *increase* in saturation. There was no clinically or statistically relevant difference between the response times of the majority of the oximeters tested. However, the Minolta and Oxyshuttle machines appeared to have long response times to a step decrease in saturation. They took an average of more than 20 s longer than other oximeters to indicate a 10% drop in saturation. The Minolta machine had an unusual response to changes in saturation, with no change for a long period and then suddenly a change of a few percent. This pattern repeated itself, so the output on the strip chart resembled a series of steps.

The response time of an oximeter depends in part on the design of the hardware. Differences in hardware, such as probe design, the stability and accuracy of the light-emitting diodes used, and the design of the circuitry, could all affect response time. The three Kontron machines, which were all identical, showed very little variation in response time regardless of the type of finger probe used. This probably indicates that for these machines, probe design has little effect on response time. Oximeters all contain microprocessors, and so software design also affects response time. Oximeter manufacturers use a smoothing algorithm that produces a "running average" of saturation over a defined period (6) or number of heart beats. The choice of algorithm is a compromise between speed of response and stability and accuracy. A long averaging period sacrifices speed of response for stability, artifact rejection, and accuracy.

Ear probes had a faster mean total response time than finger probes (Figure 5). This finding confirms Severinghaus and Naifeh's observations (1) and arises because the lung-ear circulation time is shorter than the lung-finger time. In clinical circumstances, if a rapid indication of arterial saturation is required, the ear is the obvious choice for probe site, and a rapidly responding oximeter such as a Kontron or Accusat should be used. When the same machine was compared with ear and finger probes, only two oximeters had statistically different response times. However, this was not an ideal test of the difference between probes because the ear and finger probes were tested on different individuals with differing circulation times, and this effect could not be removed.

We originally planned to use the saturation calculated from the end-tidal gas concentrations to test the accuracy of the oximeters. Severinghaus and Naifeh (1) showed calculated and measured saturations were closely correlated; however, they only performed short-term (50 s) experiments. It is obvious from Figure 5 that from about 45 s after decompression, the measured saturations and saturations calculated using Severinghaus and Naifeh's formula diverge. Assuming that the mean oximeter reading is the same as the true arterial saturation, this represents an increasing alveolar-arterial oxygen tension gradient after a rapid increase in simulated altitude, which is contrary to published results of slow decompression experiments (7,8). This may be due to either an increasing alveolar dead space or diffusion limitation of oxygen uptake. Either of these would result in an end-tidal oxygen level that was inappropriately high for the actual arterial saturation, and so the calculated saturation would be higher than the true saturation. It is not possible to separate these effects in this experiment. The practical consequence of these results is that arterial saturations calculated from end-tidal gas tensions in acute hypoxia experiments may not be accurate after about 45 s of hypoxia, and arterial blood samples will be required.

In conclusion, an ear probe should be used if an early indication of a change in arterial saturation is required. If a finger probe is used, a rapidly responding oximeter should be used with the averaging set to a minimum time period or number of heart beats and the probe placed on the thumb.

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Can Pulse Oximetry Be Used to Measure Systolic Blood Pressure?

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This study evaluates the use of pulse oximetry to accurately monitor systolic arterial blood pressure in 100 healthy volunteers. Determination of arterial blood pressure using oximetry was made at the disappearance of visual display upon blood pressure cuff inflation, at the reappearance of visual display upon cuff deflation, and by averaging the two. The blood pressures obtained by pulse oximetry were compared with the arterial blood pressures obtained by Korotokoff sounds and noninvasive blood pressure equipment. Good agreement was obtained when the average of oximetry-based systolic blood pressure estimates at the disappearance and reappearance of the waveform were compared with Korotokoff sound pressures and noninvasive equipment pressures. Thus pulse oximetry can be used to measure systolic arterial blood pressure. This technique is specifically important for patients with Takayasu's syndrome (pulseless disease) where conventional techniques often fail to monitor systolic arterial blood pressure.

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Pulse oximetry is a standard of care for general anesthesia (1). Besides providing arterial oxygen saturation, the equipment has been used in various clinical situations (e.g., assessing the efficiency of cardiopulmonary resuscitation, assessing the viability of reimplanted grafts, and as an alternative to Allen's test for ulnar artery patency) (2–4). Its use has also been reported for measurement of systolic arterial blood pressure (SBP) in patients with Takayasu's syndrome (5).

The present study was undertaken to investigate whether the plethysmographic waveform of the pulse oximeter could be utilized to measure SBP. Attempts were made to ascertain whether good agreement exists between the oximetry-derived pressures and conventional techniques used to measure SBP.

Methods

This study was conducted in 100 healthy volunteers (50 men, 50 women) after informed consent and approval by our local Committee on Human Research had been obtained. Special care was taken to ensure that individuals with a history of hypertension, diabetes mellitus, peripheral vascular disease, and renal disease were excluded from the study.

The SBP was measured by three techniques: using the plethysmographic waveform of the pulse oximeter (Ohmeda Biox 3700), by Korotokoff sound, and with oscillometric noninvasive blood pressure equipment (Colin BP 308, Mark III). The SBP was measured in the same arm for each volunteer while the subject was at rest and in the sitting position. Measurements were performed approximately 2 min apart so as to enable adequate blood flow after each recording.

An appropriate-sized blood pressure cuff attached to a sphygmomanometer was placed on one arm. The probe of the pulse oximeter was placed on the index finger on the same side; and the characteristic plethysmographic waveform, heart rate, and oxygen saturation were displayed. The visual display of plethysmography was assumed to be functioning normally once the heart rate displayed by the oximeter and the heart rate on the cardioscope corresponded. The blood pressure cuff was then gradually inflated in 2–5-mm Hg increments until the plethysmographic waveform displayed by the oximeter just disappeared. This was recorded as pressure at disappearance (BP_{DIS}). The cuff was then inflated rapidly up to 200 mm Hg and then gradually deflated in 2–5-mm Hg decrements until the plethysmographic waveform

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Table 1. Summary of Systolic Blood Pressures Recorded by Various Techniques

Technique adopted	Mean ± SD (mm Hg)
Pulse oximetry derived	
Appearance of waveform (BP_{APP})	111.1 ± 13.6
Disappearance of waveform (BP_{DIS})	119.0 ± 14.6
Average of BP_{APP} and BP_{DIS} (BP_{AV})	115.1 ± 13.4
Korotokoff sounds (BP_K)	115.5 ± 13.2
Noninvasive oscillometric blood pressure equipment (BP_{NI})	115.9 ± 11.6

Table 2. Correlation Coefficients of Pulse Oximetry-Based Systolic Blood Pressure Estimates With BP_K and BP_{NI}

	BP_{DIS}	BP_{APP}	BP_{AV}
BP_K	0.8627	0.7919	0.8714
BP_{NI}	0.8256	0.7841	0.8472

BP_{DIS}, blood pressure readings at disappearance of oximeter waveform upon cuff inflation; BP_{APP}, blood pressure readings at appearance of oximeter waveform upon cuff deflation; BP_{AV}, calculated average of BP_{DIS} and BP_{APP}; BP_K, blood pressure reading by Korotokoff sounds; BP_{NI}, blood pressure reading by oscillometric noninvasive blood pressure equipment.

reappeared on the visual display. This was recorded as pressure on appearance of the waveform (BP_{APP}).

Lawson et al. (6) observed that the oximeter function ceased once the occluding pressure during inflation reduced the relative blood flow to 8.6% of the original blood flow. A relative flow of only 4% of the baseline was required to restart the oximeter function. Thus for the oximeter to detect signals, the relative blood flows during inflation and deflation were different. Therefore, the average value of BP_{DIS} and BP_{APP} was calculated and recorded as BP_{AV}.

The SBP was also measured in the same arm by auscultation of Korotokoff sounds. The measurement was made by the same observer (who was not aware of the SBP readings obtained by oximetry) and was recorded as BP_K. The last reading of SBP was obtained using oscillometric noninvasive blood pressure equipment (Colin BP 308, Mark III), and the pressure was recorded as BP_{NI}.

Thus, using these techniques, four blood pressure readings were recorded for each subject, viz. BP_{DIS}, BP_{APP}, BP_K, and BP_{NI}, and an average (BP_{AV}) was calculated as (BP_{DIS} + BP_{APP})/2. Realizing that the issue at hand was not correlation but agreement, techniques proposed by Bland and Altman (7) were used to evaluate the extent of agreement between various methods. Attempts were also made to estimate the error in measuring SBP by pulse oximetry.

Results

The study was conducted in 100 volunteers (age 20–62 yr). Table 1 shows the mean and standard deviation of the SBPs recorded by the various techniques. Only normotensive individuals were included in the study. One of the female volunteers who was found to be hypertensive during this study (BP_{DIS}, 176 mm Hg; BP_{APP}, 170 mm Hg; BP_{AV}, 173 mm Hg; BP_K, 170 mm Hg; BP_{NI}, 171 mm Hg) was excluded and replaced with a normotensive volunteer. None of the mean differences between the pulse-oximetry based estimates and conventional readings was statistically different between men and women ($P > 0.05$), except for the differences between BP_{APP} and BP_{NI} ($P < 0.05$). The results for both the sexes therefore have been combined in the presentation below.

The Pearson's correlation coefficients between the pulse oximetry-based blood pressure estimates and BP_K and BP_{NI} readings are shown in Table 2. These are recorded to facilitate comparison with previous studies that used correlation as a measure. The objective is not to evaluate correlation but to evaluate agreement, which is a step beyond. For this, we studied the differences in readings obtained by various techniques and assessed whether they were small enough to justify the use of oximetry estimates in place of BP_K and BP_{NI}. Table 3 summarizes statistics on the relevant differences. The last two rows of the table show that the differences between BP_{AV} and BP_K or BP_{NI} were as often positive as negative, and the mean differences were close to an ideal zero. In fact, only these mean differences were not significantly different from zero ($P > 0.5$); all other differences were highly significant ($P < 0.01$).

If BP_{AV} was in real agreement with either BP_K or BP_{NI}, then the regressions, when forced through the origin, should yield a regression coefficient of 1 (so that the regression is of the type $Y = X$). Table 4 shows that this indeed is true. In line with the observations in Table 4, it is evident that the regression coefficients for BP_{DIS} are less than 1, for BP_{APP} more than 1, and for BP_{AV} equal to 1. The scatter plots of BP_K with BP_{AV} and of BP_{NI} with BP_{AV} are shown in Figures 1 and 2, respectively. As there is high variability, 95% confidence bands for each regression line are also shown.

The results obtained indicate that BP_{AV} is closer to BP_K and BP_{NI} than either BP_{DIS} or BP_{APP}. The zero mean differences and unit regression coefficients indicate that on average BP_{AV} can be substituted for BP_K and BP_{NI}. Kolmogorov Smirnov's test done through the SPSS package revealed that these distributions are not significantly different ($P > 0.2$ in each case) from the Gaussian type with mean = 0 and SD = 7. A Gaussian distribution with mean = 0 and SD = 7 of the differences between BP_{AV}, BP_K, and BP_{NI}

Table 3. Summarizing Statistics on Differences Between Pulse Oximetry-Based Readings and Readings Obtained by Conventional Methods

Differences	n (+ve, 0, −ve)	Mean difference	SD of difference	Minimum difference	Maximum difference
$BP_{DIS} - BP_K$	100 (65,12,23)	3.5[a]	7.38	−18	20
$BP_{DIS} - BP_{NI}$	100 (63,5,32)	3.1[a]	8.22	−14	20
$BP_{APP} - BP_K$	100 (24,15,61)	−4.4[a]	8.55	−40	10
$BP_{APP} - BP_{NI}$	100 (29,8,63)	−4.9[a]	8.42	−32	10
$BP_{AV} - BP_K$	100 (44,12,44)	−0.4	6.69	−24	15
$BP_{AV} - BP_{NI}$	100 (47,7,46)	−0.9	7.09	−22	13

BP_{DIS}, blood pressure readings at disappearance of oximeter waveform upon cuff inflation; BP_{APP}, blood pressure readings at appearance of oximeter waveform upon cuff deflation; BP_{AV}, calculated average of BP_{DIS} and BP_{APP}; BP_K, blood pressure reading by Korotokoff sounds; BP_{NI}, blood pressure reading by oscillometric noninvasive blood pressure equipment; +ve, positive; −ve, negative.

[a] Highly significant difference from zero ($P < 0.01$).

Table 4. Regression Coefficient When Regression Is Passed Through Origin

Pulse oximetry readings	Conventional readings BP_K	Conventional readings BP_{NI}
BP_{DIS}	0.967	0.970
BP_{APP}	1.035	1.038
BP_{AV}	1.002	1.004

BP_{DIS}, blood pressure readings at disappearance of oximeter waveform upon cuff inflation; BP_{APP}, blood pressure readings at appearance of oximeter waveform upon cuff deflation; BP_{AV}, calculated average of BP_{DIS} and BP_{APP}; BP_K, blood pressure reading by Korotokoff sounds; BP_{NI}, blood pressure reading by oscillometric noninvasive blood pressure equipment.

indicates that nearly 95% of the differences would be within ±14 mm Hg.

Discussion

Pulse oximetry is increasingly being used today to assess the hemodynamic status of patients (2–4). Its use as a measure of SBP in normal patients and in patients with Takayasu's syndrome has also been reported (5,8,9). However, the methodology adopted in these studies has been conflicting, and using statistical analysis, attempts have been made to show a good correlation instead of agreement.

Whereas Wallace et al. (8) (in their study of 51 patients) recorded SBP when the oximeter lost its visual display during blood pressure cuff inflation (BP_{DIS}), Talke et al. (9) (in a study on 20 healthy volunteers and 42 anesthetized patients) recorded blood pressure when the visual display of the plethysmographic waveform just reappeared upon cuff deflation (BP_{APP}). In the present study, BP_{DIS} is generally higher than BP_{APP}. This is probably because of relative difference in blood flow during inflation and deflation, being 8.6% of the original flow during inflation and 4% on cuff deflation (6). It was also observed that BP_K and BP_{AV} show close agreement, suggesting that the flow during measurement of BP_K is somewhere near the average of 4% and 8.6% of the original blood flow.

In the present study, attempts were made to investigate whether the pressure at disappearance of the plethymographic waveform upon cuff inflation (BP_{DIS}), pressure at reappearance of the waveform upon cuff deflation (BP_{APP}), or the average of these two is an accurate indicator of SBP in healthy Indian subjects.

Good correlation was observed when BP_{DIS} was compared with BP_K and BP_{NI} ($r = 0.8627$ and $r = 0.8256$, respectively). Good correlation was also observed on comparing BP_{APP} with BP_K and BP_{NI} ($r = 0.7919$ and $r = 0.7841$, respectively). However, the correlation was best observed when BP_{AV} was compared with BP_K and BP_{NI} ($r = 0.8714$ and $r = 0.8472$, respectively).

Wallace et al. (8) observed good correlation between BP_{DIS} and the Doppler method ($r = 0.93$). However, in their study, 729 pairs of SBPs were obtained in 51 patients, suggesting that blood pressure was repeatedly monitored in each subject. This could partly explain the high correlation observed in their study. Talke et al. (9) in their study observed a better correlation between BP_{APP} and BP_K ($r = 0.958$). However, their study comprised only 20 volunteers.

As has been emphasized by Bland and Altman (7), high correlations do not justify substituting one value for the other. Talke et al. (9) reported a regression equation of $y = 0.875x + 15.1$, where y represents BP_K and x represents BP_{APP}. Notwithstanding high

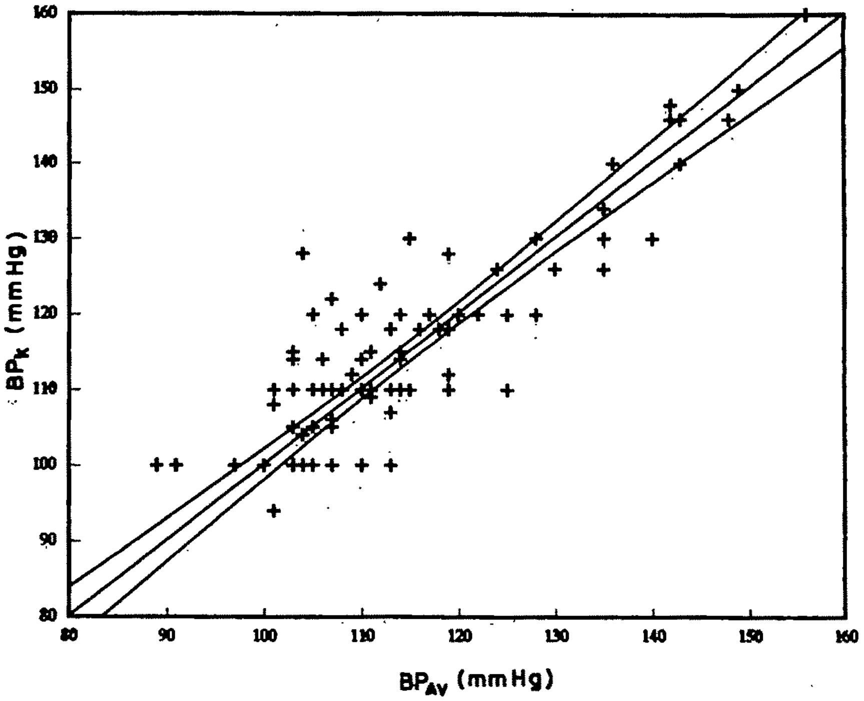

Figure 1. Scatter plot regression line and confidence band of Korotokoff sounds (BP_K) versus average of BP_{DIS} and BP_{APP} (BP_{AV}).

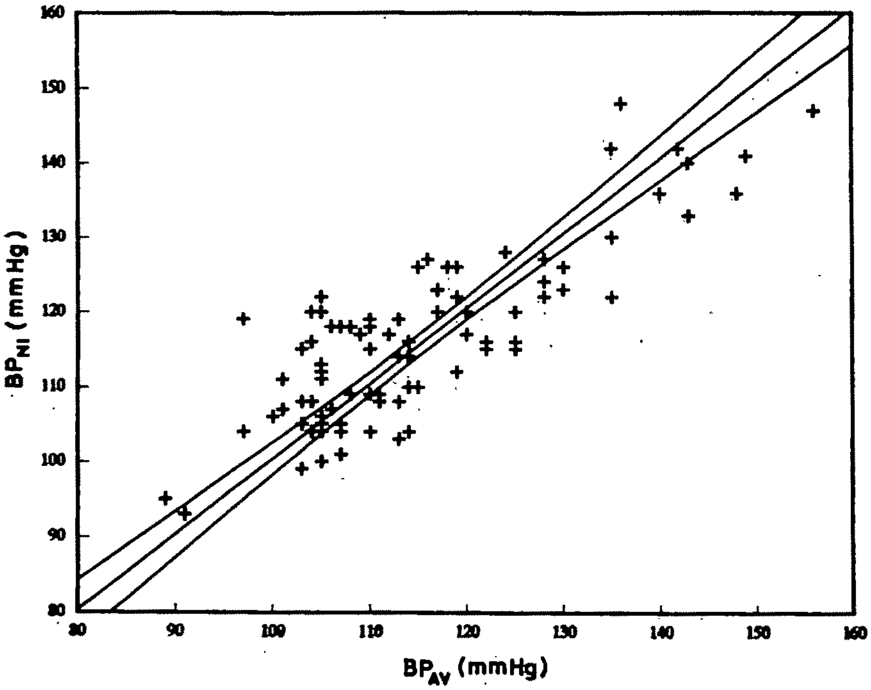

Figure 2. Scatter plot regression line and confidence band of noninvasive oscillometric blood pressure equipment (BP_{NI}) versus average of BP_{DIS} and BP_{APP} (BP_{AV}).

correlation, large values of intercept and a regression coefficient substantially less than 1 indicate that the relationship is far from $y = x$. This applies to all the relationships they have investigated. Thus, their conclusion that BP_{APP} can be used to accurately measure SBP is not valid because good agreement has not been established in so far as their analysis goes. This is also true for other reported studies (8,9).

We have been able to show that oximetry readings can in fact be used to measure SBP. But these are neither BP_{DIS} nor BP_{APP}. It is the BP_{AV} that very closely agrees with the level measured by conventional methods (BP_K and BP_{NI}).

In nearly 95% of the cases, the differences between BP_{AV} and conventional methods are likely to be within ±14 mm Hg. It is interesting to observe that the difference between BP_K and BP_{NI} had SD = 6.53 (mean difference = 0.38). Thus even when these two methods are used, the 95% limits on difference are ±13 mm Hg. This shows that BP_{AV} readings were almost as close to BP_K measurements as BP_K measurements are to BP_{NI}. An error of 14 mm Hg in SBP can be accepted clinically.

Blood flow signals displayed by Doppler probe have been used to measure SBP and to assess peripheral perfusion in patients with Takayasu's syndrome (5). Flow signals and plethysmographic waveform can also be detected by oximetry in limbs with weak or absent pulses (10), and this may be utilized to measure SBP. The present study demonstrates that the plethysmographic waveform can be used to measure SBP, with best agreement between BP_{AV} and BP_K or BP_{AV} and BP_{NI} confirming the reliability of this technique.

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Heparinase in the Activated Clotting Time Assay: Monitoring Heparin-Independent Alterations in Coagulation Function

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The activated clotting time (ACT) is routinely used to monitor heparin during cardiopulmonary bypass surgery. Activated clotting times may be influenced by a number of factors other than heparin. The presence of heparin in blood samples disguises the occurrence of non-heparin-related changes in coagulation function. During cardiopulmonary bypass, it is difficult to ascertain baseline clotting time fluctuations with ACT alone. Previous attempts to establish accurate baseline data were imprecise and involved extensive sample handling. In this study, we present data obtained using a modified (ACT) assay that incorporates heparinase. The heparinase test cartridge (HTC) instantaneously, specifically, and completely removes heparin in the blood sample at the initiation of the test. In conjunction with standard ACT techniques, the clinician is provided with heparin-independent (baseline) and functional clotting data. The HTC/ACT assay was used in a case study involving 19 patients undergoing cardiopulmonary bypass surgery. The data gathered indicate the usefulness of this assay in monitoring incidents of baseline drift, hemodilution, and hypercoagulation and the efficacy of protamine reversal.

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Activated clotting time (ACT) assays are routinely used to monitor the anticoagulant effects of heparin during cardiovascular surgery. Activated clotting time measurements are taken (a) before the administration of heparin to establish the patient's baseline (heparin-independent) clotting time and (b) periodically during cardiopulmonary bypass (CPB) to ensure adequate heparinization (1,2). The ACT values are also used to monitor the neutralization of heparin by protamine where a return to preoperative ACT is typically used as the target value.

The ACT is a functional measure of the intrinsic clotting pathway (3), which may be influenced by factors other than heparin. Cardiovascular surgical procedures and extracorporeal circulation may lead to incidents of platelet dysfunction (4), hemodilution (5), disseminated intravascular coagulation, or hypercoagulation (6). These occurrences potentially alter the baseline clotting time during the course of an operation. Therefore, assuming a constant baseline ACT equivalent to the preoperative value may lead to inaccurate conclusions concerning the administration of heparin or protamine. For example, hemodilution results in an extended ACT and may lead to an overestimate of the quantity of protamine required for neutralization. Conversely, hypercoagulation, resulting in a shortened ACT, may lead to an underestimate of the quantity of protamine required for neutralization (7).

The presence of heparin in blood samples prevents the measurement of baseline clotting times by a standard ACT assay. The expeditious pretreatment of samples to remove heparin before the determination of ACT would allow for the procurement of baseline clotting information, even on samples taken from patients receiving heparin. The concept of using heparinase to neutralize enzymatically the anticoagulant properties of heparin before coagulation testing was put forth by Hutt and Kingdon in 1972 (8). However, the widespread availability of heparinase for this application was delayed until methods for producing the enzyme were refined (9,10). Recently, the heparinase test cartridge (HTC), a variation of the ACT assay, has been developed. The assay incorporates a bacterial heparinase into one of the two cartridge channels of the dual-channel high-range

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ACT (HR ACT) test manufactured by Medtronic HemoTec, Inc. (Englewood, Colo.). Heparinase eliminates the anticoagulant effect of heparin at the onset of the test. The clinician is thus provided with baseline (heparinase channel, HTC) and functional (untreated channel, HR ACT) clotting-time information. Salmenpera et al. (11) used heparinase in ACT tests to evaluate the occurrence of heparin rebound after CPB operations. In addition, this test is intended to provide answers to the following questions: (a) Is heparin present before surgery? (b) Has the baseline clotting time varied during the procedure? (c) Is heparin present after protamine reversal?

The primary focus of this investigation was to evaluate the performance of the HTC test in giving baseline clotting-time information during CPB surgery. This report presents HTC results obtained during a study that included 19 patients having CPB. The results presented here indicate the frequent occurrence of baseline clotting deviations and the usefulness of the HTC test in monitoring these deviations.

Methods

Nineteen patients undergoing routine CPB at the Sunnybrook Medical Center in Toronto from June 26 to July 13, 1990, comprised the study group. There were 16 men and 3 women in the group, which ranged in age from 31 to 74 yr (average, 56 yr). Surgical procedures included 15 coronary arterial bypass grafts (CABG), three atrial valve replacements (AVR), and one combined procedure (CABG/AVR). The patients were randomly chosen for this study according to the order of their presentation into the surgical suite and on no other basis. Heparinase ACT tests were performed on surplus aliquots of blood samples drawn for routine analysis. The results were not used to calculate heparin or protamine administration in this study. Formal human subject approvals were not required for this study.

Cardiopulmonary bypass was established after the infusion of heparin (300 IU/kg). Additional 5000-IU heparin boluses were infused as required to maintain an ACT greater than 400 s. Beef lung heparin (UpJohn, Kalamazoo, Mich.) was used in all procedures. Protamine sulfate (3.1 ± 0.8 mg/kg) was infused at the conclusion of CPB to reverse the effects of heparin. An additional dose of protamine was given if the ACT did not return to presurgical levels after the first injection.

The heparinase HR ACT cartridges (IBEX Technologies, Montreal, Canada/Medtronic HemoTec, Inc., Englewood, Colo.) were used to monitor coagulation times. The HTCs are designed to be used with the dual-channel Automated Clotting Timer instrument (Medtronic-HemoTec). Tests were performed on fresh whole blood samples taken before CPB, within 10 min after heparinization, every 20 to 30 min after heparinization, and after protamine reversal. The assay was carried out by transferring 0.4 mL of fresh whole blood into each of the two channels of a cartridge that had been prewarmed at 37°C for 3–5 min. The cartridge was immediately placed in the timer instrument, and the test was started by pulling the actuator cover forward. The procedure is identical to that used for standard HR ACT assays.

Preoperative activated partial thromboplastin times (aPTT) and prothrombin times were also noted.

Blood samples were taken before heparinization, within 10 min after heparinization, every 20 to 30 min after heparinization, and after protamine reversal, and were immediately analyzed for hematocrit and hemoglobin content. The blood volume before operation was estimated according to the following equation:

$$V\ (\mathrm{L}) = \text{Body weight (kg)} \times 0.068\ (12)$$

The addition and collection of all fluids and their sampling times were recorded.

Correlations between heparinase HR ACT values and those of estimated blood volume, hematocrit, and hemoglobin were analyzed. All values were normalized with respect to the preoperative values and correlation coefficients derived by direct computation using the linear least-squares method (13).

Results

Individual patient profiles are summarized in Table 1. In all 19 patients, preoperative ACT and HTC times were equivalent within the accuracy of the test (±12%). The average differential between these readings was 3.3 s with the greatest difference being 12 s. Four patients in this study were referred to surgery with abnormally high aPTT values (>35 s). However, HTC values indicate that the extended aPTT in these patients was not due to the presence of heparin.

The average HTC/ACT differential in the readings after protamine reversal (postprotamine) was 2.6 s, with the greatest difference being 7 s. These readings are equivalent within the accuracy of the instrument, indicating that the protamine reversal after CPB was complete in each patient. The average HTC/ACT values are illustrated in Figure 1. This diagram demonstrates the equivalence of the two tests at the prebypass and postprotamine points. Prebypass HTC and ACT values were 123.6 ± 10.6 and 122.8 ± 12.4 s, respectively. Postprotamine HTC and ACT values were 97.6 ± 10.8 and 97.7 ± 11.7 s, respectively.

Figure 1 also illustrates two trends observed in this study. The first occurs during bypass in which baseline clotting times (HTC result) are extended an

Table 1. Individual Patient Profiles

Patient No.	Procedure	Sex	Age (yr)	Weight (kg)	aPTT (s)	PT (s)	Preop Hct (%)	Preop Hbg (g%)	Preop ACT (s)	Preop heparinase ACT (s)	Total heparin (IU)	Protamine (mg)	Maximum baseline deviation (s)	Postprotamine baseline deviation (s)
1	AVR	F	31	62	38.2	11.5	35	11.5	126	126	25,000	200	54	−29
2	CABG	M	58	82	27.1	10.9	39	13.1	128	126	34,000	200	22	−31
3	CABG	M	71	81	27.1	10.1	41	13.9	115	111	45,000	300	21	1
4	CABG	M	39	86	53.1	11.0	40	13.9	119	110	55,000	300	35	−13
5	AVR	M	32	96	28.8	10.2	40	14.1	123	122	35,000	250	47	−28
6	CABG	M	43	109	49.0	18.1	38	13.4	119	118	40,000	400	50	−21
7	CABG/AVR	M	67	63	30.5	9.8	44	15.3	138	138	30,000	350	41	−30
8	CABG	M	72	94	28.0	10.2	31	10.2	146	148	35,000	200	34	−34
9	CABG	F	72	75	28.0	10.2	31	10.2	129	125	28,000	250	27	−45
10	CABG	M	53	82	25.3	10.0	42	14.7	105	110	42,000	300	34	−16
11	CABG	M	62	87	30.9	10.2	41	14.7	129	126	35,000	200	30	−20
12	CABG × 2	M	45	87	29.1	10.1	42	14.3	129	124	32,000	250	36	−37
13	CABG	M	62	73	28.5	9.8	43	15.6	122	120	33,000	250	39	−10
14	CABG	M	59	81	42.5	10.0	43	15.3	118	112	50,000	300	36	−35
15	CABG × 2	M	63	78	32.2	10.6	39	13.4	142	154	39,000	300	42	−64
16	AVR	M	56	88	28.5	10.0	48	16.5	114	112	38,000	250	29	−24
17	CABG	F	74	75	25.1	9.8	36	11.9	108	111	37,000	250	28	−19
18	CABG	M	51	76	29.7	9.7	46	16.0	120	120	30,000	250	57	−11
19	CABG	M	63	77	27.4	10.2	42	14.7	119	121	28,000	250	54	−12

aPTT, activated partial thromboplastin time; PT, prothrombin time; Hct, hematocrit; Hbg, hemoglobin; ACT, activated clotting time; AVR, atrial valve replacement; CABG, coronary artery bypass grafting.

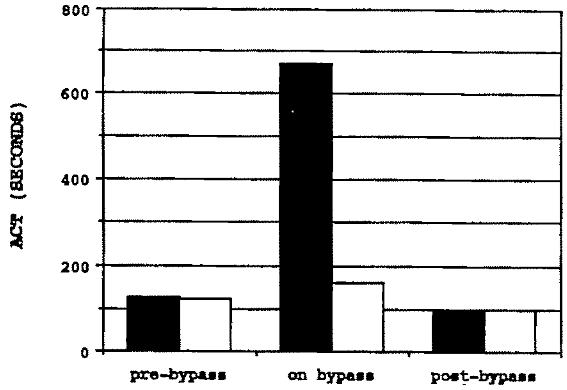

Figure 1. The average values of heparinase test cartridge (HCT) and activated clotting time (ACT) taken from 19 patients before bypass (123.6 ± 10.6, 122.8 ± 12.4), during bypass (149.3 ± 21.1, 655.1 ± 138.2), and after protamine reversal (97.6 ± 10.8, 97.7 ± 11.7). The HTC (*white column*) and ACT (*black column*) were measured at various times during CPB.

Table 2. Correlation Factors for Heparinase HR ACT Values

Patient No.	Estimated blood volume (r)	Hematocrit (*r*)	Hemoglobin (*r*)
1	0.83	0.86	0.87
2	0.75	0.70	0.70
3	0.75	0.81	0.81
4	0.73	0.90	0.90
5	0.18	0.50	0.47
6	0.81	0.83	0.84
7	0.00	0.51	0.51
8	0.53	0.72	0.68
9	0.56	1.00	1.00
10	0.93	0.93	0.94
11	0.99	0.94	0.94
12	0.51	0.80	0.77
13	0.73	0.82	0.81
14	0.52	0.87	ND
15	0.00	0.19	0.17
16	0.70	0.92	0.94
17	0.87	1.00	1.00
18	0.78	0.97	0.97
19	1.00	1.00	1.00
Average	0.64	0.80	0.80

average of 37.7 ± 10.8 s. This represents a significant deviation from prebypass baseline values, demonstrating a slight but measurable decrease in coagulation capacity during the procedures. Blood volumes of patients were increased by pump prime, cardioplegic, and other solutions an average of 50%. Therefore, the hemodilution effect is suspect in causing an upward drift in baseline clotting times. The correlations for HTC values with estimated blood volume, hematocrit, and hemoglobin for each patient are listed in Table 2. The average correlations for the study group are $r = 0.64$, $r = 0.80$, and $r = 0.80$ for blood volume, hematocrit, and hemoglobin, respectively.

The second trend observed in this study was the decreased postprotamine clotting time. On average, the postprotamine clotting time was 25.2 ± 14.7 s shorter than at prebypass.

Discussion

The ACT test has become a standard measure of the effectiveness of heparin during CPB. The assay is valuable in assessing the functional coagulation of patients while they are on heparin therapy. However, the presence of heparin in blood samples prevents the determination of changes in the patient's normal coagulation function that may occur during the procedure. These alterations, which include hemodilution and hypercoagulation, are frequently induced by the procedure itself.

Researchers have attempted to obtain accurate baseline clotting information on heparinized samples by a variety of means. Previous attempts have included the use of ion exchange resins and protamine titration (14) to remove heparin selectively. Ion exchange resins tend to interfere with coagulation measurements, and protamine titration, although more accurate, is costly and time-consuming. Recently, a heparinase ACT assay has been developed to provide rapid and accurate baseline clotting information on heparinized whole blood samples. The assay consists essentially of a standard HR ACT assay in which heparin is completely neutralized at the onset of the test by the action of a bacterial heparinase. In this format, the heparin neutralization function is invisible to the user.

This report constitutes one of the first studies in which baseline clotting times were routinely monitored in a clinical setting. In this study, all prebypass HTC and ACT results were equivalent, indicating that heparin was not present in any patient before operation. Four patients in this study had preoperative aPTT values higher than normal. The combination of preoperative HTC/ACT differentials and aPTT absolute values allows for the identification of potential non-heparin-related coagulopathies that may be resolved by further analysis. This information will alert clinicians to a predisposition for postoperative bleeding occurrences that may have to be resolved by a method other than heparin/protamine therapy.

The data indicate the use of this assay to monitor hemodilution while the patient is on heparin therapy. In 18 of the 19 patients reported on here, an extended baseline clotting time during the bypass procedure was observed. Correlation with blood volume, hematocrit, and hemoglobin data indicate that the extended baseline clotting time may be due to hemodilution. In this study, coagulation function was not severely compromised after protamine administration. However, the correlation between dilution and baseline deviation suggests that the ability to rapidly obtain baseline clotting information will alert clinicians of the potential for postoperative complications caused by dilution. These postoperative complications may occur more frequently when treating patients with lesser blood volume, such as children and small adults, or patients with a diminished concentration of platelets or of clotting factor proteins (15).

Postbypass data confirmed the effectiveness of protamine neutralization in all 19 cases. We also observed a consistent decrease in postprotamine clotting times compared with prebypass values. This effect has been noted in previous studies (16,17) and may be due to the activation of clotting resulting from some aspect of the surgical procedure (7). Recently, Gravlee et al. (18) demonstrated that ACT values taken during the period between surgical incision and heparin administration closely approximate postprotamine ACT values. The HTC test used in this study will facilitate the determination of baseline ACT at any point in the surgical procedure. It is apparent that the HTC assay data could be used to determine more accurately the quantity of protamine required for reversal. The average protamine dose used was 3.2 mg/kg but ranged from 2.1 to 5.5 mg/kg. The use of HTC assays to confirm neutralization could reduce the amount of protamine used and could diminish associated complications. Similarly, the HTC assay will aid in the assessment of heparin rebound occurrences in the intensive care unit, which often result from plasma transfusion (19).

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Acute Colloid Administration Increases Ischemia in the Myocardium Supplied by a Stenotic Coronary Artery

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The effect of acute colloid administration was evaluated in the pig heart in which an external coronary artery stenosis was applied. Seven pigs received thiopentone and halothane anesthesia. Ultrasonic crystals were inserted in the myocardium supplied by the left anterior descending (LAD) and circumflex coronary arteries. Left ventricular pressure was measured and regional myocardial function was quantified with the pressure-length loop and the end-systolic pressure-length ratio. A significant stenosis was applied to the LAD artery, after which the animal received fixed colloids to increase the left ventricular end-diastolic pressure. Regional myocardial ischemia was defined with reference to postsystolic shortening and lactate production from the region supplied by the LAD artery. The application of the stenosis caused an increase in postsystolic shortening from 9.62% ± 4.24% to 26.12% ± 5.81% (mean ± SEM; $P < 0.05$), and lactate extraction changed from 15.88% ± 2.38% to −9.56% ± 5.32% ($P < 0.05$). Acute colloid administration increased the left ventricular end-diastolic pressure from 9.71 ± 1.77 to 15.93 ± 2.07 mm Hg ($P < 0.05$), and lactate extraction further decreased to −76.63% ± 19.19% ($P < 0.05$). Postsystolic shortening increased to 36.22% ± 5.10% ($P < 0.05$). The oxygen tension in the venous blood draining the LAD region decreased from 36.74 ± 9.37 to 17.34 ± 1.23 mm Hg ($P < 0.05$). We conclude that in the acute pig model, augmentation of the preload worsens regional myocardial ischemia in an area supplied by a stenotic coronary artery.

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Left ventricular coronary blood flow (CBF) occurs mainly in diastole, and the driving pressure is approximated by the difference between the diastolic aortic pressure and the left ventricular end-diastolic pressure (LVEDP) (1,2). If LVEDP increases, as could occur during acute colloid administration, the driving pressure will decrease (if aortic pressure remains unchanged). Autoregulation will preserve CBF during such changes in perfusion pressure if the coronary arteries are normal (3). However, if autoregulation is exhausted, it is possible that subendocardial ischemia could occur if the LVEDP is raised, and there is indeed clinical evidence suggesting that acute colloid administration in patients with ischemic heart disease precipitates myocardial ischemia (4).

This study was therefore designed to evaluate the effect of acute colloid administration during general anesthesia on regional myocardial function in left ventricular (LV) segments supplied by a normal and a narrowed coronary artery.

Methods

Permission for the study was obtained from the Ethical Committee of the University, and the animals were cared for according to national and university guidelines.

Seven pigs (25–29 kg) were used. The animals were premedicated with intramuscular ketamine (5 mg/kg). An intravenous infusion was started, and anesthesia was induced with 7 mg/kg of thiopental. A tracheostomy was performed, the trachea was intubated, and ventilation was controlled using 40% oxygen and 60% nitrogen. The ventilatory frequency was kept constant at 8 breaths/min, and the tidal volume was adjusted to maintain the arterial carbon dioxide tension (Pa_{CO_2}) at 35–39 mm Hg. Anesthesia was maintained for the duration of the operation with 1% halothane. Skeletal muscle paralysis was obtained with pancuronium (initially 0.1 mg/kg) and was maintained with an infusion of pancuronium ($0.01\ mg \cdot kg^{-1} \cdot h^{-1}$).

Temperature was maintained between 36.3 and 37.2°C with an under-table heating device. Normal

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saline was infused at a rate of 5 $mL \cdot kg^{-1} \cdot h^{-1}$ for the duration of the experiment.

Through a neck incision, a pulmonary artery catheter (Edward Laboratories Inc.) was inserted into the internal jugular vein and floated into the pulmonary artery. The correct position of the catheter was verified once the chest was opened, and the injection port was shown to be in the right atrium at postmortem dissection. Five milliliters of 5% dextrose at 4°C was injected by hand into the proximal injection port, and a cardiac output computer (Mansfield 9530) calculated the cardiac output. Injections were spaced throughout the respiratory cycle, and the cardiac output was determined in triplicate. A 16-gauge stiff cannula was inserted into the internal carotid artery and was advanced into the proximal aorta, 1 cm distal to the aortic valve. The catheter was connected to a pressure transducer (Statham, natural frequency 50.3 Hz) for the determination of aortic blood pressure.

A balloon-tipped catheter (Fogarty 8/14, Edward Laboratories) was inserted into the femoral artery and was positioned in the descending aorta at the level of the diaphragm. This catheter was used to momentarily increase aortic pressure in order to increase LV pressure for the determination of the LV end-systolic pressure-length relationship.

A left thoracotomy was performed, and the pericardium was opened. A stiff short 16-gauge cannula was sutured into the LV cavity for the measurement of LV pressure with a pressure transducer (Statham, natural frequency 50.6 Hz). The LV end-systolic pressure was defined as the LV pressure at the time that the LV end-systolic pressure-length relationship was at a maximum.

Two pairs of piezoelectric crystals were positioned in the subendocardium (5). One pair was placed in the region supplied by the left anterior descending coronary artery (LAD) and the other pair, in the region supplied by the circumflex coronary artery (LX) (6). The signals were processed (Ultrasonic Dimension System, Schuesler); and the maximum segment length (Lmax), minimum segment length (Lmin), and regional shortening during systole (dL = Lmax − Lmin) were obtained. The latter was normalized for Lmax (dL% = dL/Lmax × 100). Lmax was taken at the time the sharp upslope of the LV pressure started, and Lmin was measured when the aortic valve was closed. Postsystolic shortening (PSS) was defined as regional shortening that occurred after the aortic valve closed and was expressed as a percentage of the total systolic shortening (7).

The LAD was dissected free from the underlying myocardium and a 3.0 silk suture was looped around the artery. This was connected to a micrometer-controlled snare, which allowed for graded constriction of the coronary artery. To create a fixed constriction, the snare was tightened in increments every 5 min until regional systolic dysfunction was observed. The degree of constriction was noted, and the snare was released for 15 min. The snare was then reapplied to a point short of what has previously been associated with dysfunction. By repeating this procedure, CBF could be reduced to the point where no resting systolic dysfunction occurred although diastolic dysfunction (i.e., PSS) was present. At this point, previous work has indicated that CBF will be reduced in the order of 40% (8–11).

A 20-gauge cannula was inserted into a vein draining the LAD region. Blood from this area was analyzed for blood gas levels and lactate concentration.

The LV pressure signal and regional systolic movement were combined on an oscilloscope (Tektronix) for the continuous display of pressure-length loops for both the LAD and LX regions. Data were recorded directly by microcomputer sampling at 200 Hz for 5 s after the animal was removed from the ventilator for 15 s. Data were stored on floppy disk for analysis. Calibration of transducers was performed before and during the experiments, and the zero level was taken at the level of the LV apex. Arterial and coronary vein blood were analyzed for gas levels and lactate concentration during the various experimental steps (IL Cooximeter, IL 613 Bloodgas Analyzer, Instrumental Laboratories). Lactate extraction was defined as the arterial minus venous blood lactate concentration normalized for arterial lactate concentration and expressed as a percentage. A positive value implies lactate extraction, and a negative value indicates lactate production.

The mean arterial pressure was calculated by computer from the area under the aortic pressure recording, and the heart rate was determined from the ventricular pressure recording. Myocardial contractility was determined by the end-systolic pressure-length relationship (Ees) (12,13). This was obtained by stepwise partial occlusion of the aorta over 5–7 beats with the occlusion catheter. For each of these beats, the computer determined the maximum pressure-length ratio from the start of systole; and these pressure and length points, which coincided with the end of systole, were subjected to linear regression analysis. (The slope of this regression is defined as the Ees, and the intercept of Ees on the length axis [X-axis] is abbreviated as L_0 [mm].) Regional myocardial work was obtained by integrating the area within the pressure-length loop (mm Hg·mm). Global LV stroke work was calculated as the product of mean arterial pressure and stroke volume (mm Hg·mL).

Arterial oxygen concentration (Ca_{O_2}) and LAD venous blood oxygen content (Cv_{O_2}) were calculated from the following equation: ($1.39 \times S_{O_2}/100 \times Hb$) +

Table 1. General Hemodynamics

	Control	Constriction	Volume
HR (beats/min)	115.00 ± 4.96	116.81 ± 3.72	114.11 ± 4.11
MAP (mm Hg)	77.39 ± 6.46	68.34 ± 6.05	80.21 ± 5.18
LVEDP (mm Hg)	9.69 ± 1.24	9.71 ± 1.77	15.93 ± 2.07[a]
SV (mL)	22.51 ± 0.71	22.26 ± 0.80	26.00 ± 1.00[a]
CO (L/min)	2.59 ± 0.13	2.60 ± 0.10	2.95 ± 0.08[a]
LVSW (mm Hg/mL)	1737.47 ± 151.87	1521.25 ± 152.91	2087.01 ± 165.49

Control, values obtained before the application of the constriction to the left anterior descending coronary artery; Constriction, values obtained after constriction; Volume, values recorded after colloid administration; HR, heart rate; MAP, mean arterial pressure; LVEDP, left ventricular end-diastolic pressure; SV, stroke volume; CO, cardiac output; LVSW, left ventricular stroke work.

Values are mean ± SEM for seven animals.

[a] $P < 0.05$ for comparison of constriction and volume phases.

$(0.0031 \times Po_2)$, where So_2 is oxygen saturation and Po_2 is oxygen tension. The coefficient of oxygen delivery (COD) was derived from the equation COD = $Cao_2/(Cao_2 - Cvo_2)$.

After completion of the operation, the halothane concentration was reduced to 0.5% for 30 min after which control values were recorded (CONTROL). The stenosis then was applied to the LAD artery and variables were recorded after 30 min (CONSTRICTION). Gelatin polypeptide (Haemocel, Hoechst) was given at a rate of 50 mL · every 10 min until LVEDP increased by 100% of that obtained at the CONSTRICTION phase or a decrease in myocardial lactate extraction of more than 10% was demonstrated. Data were then recorded (VOLUME).

In addition, four pigs were subjected to similar surgical preparation. Preconstriction data were recorded, and constriction to the LAD artery was applied as described. The preparation was then left for 120 min, and data were recorded at 60 and 120 min.

Data were initially analyzed with analysis of variance (Tukey) and were tested for homogeneity with the multiple-range test. A confidence level of 0.05 was accepted as indicative of statistical differences when CONTROL was compared with the CONSTRICTION and the CONSTRICTION was compared with VOLUME.

Results

Application of the constriction to the LAD artery did not result in global hemodynamic changes (Table 1). On a regional level, the systolic function (Ees) of both the LAD region, i.e., the segment supplied by the stenosed coronary artery, and the region supplied by the LX artery (normal segment) did not change. In the LAD region, the PSS did increase ($P < 0.05$), and in the LX region, PSS remained unaltered (Table 2). The CO_2 tension in the blood draining the LAD segment increased, and the extraction of lactate, registered during the control phase, changed to lactate production after the application of the constriction (Table 3).

Taken in combination, the significant change in lactate dynamics and PSS suggest that the degree of constriction applied to the LAD was significant although not sufficient to cause resting systolic dysfunction.

The aim of doubling the LVEDP with colloid administration was not realized in a single animal (average total volume of gelatin polypeptide given, 8 mL/kg). Further changes in the PSS were observed in all seven animals before the LVEDP increased by 100%. The ischemic changes were confirmed by a significant increase in lactate production from the LAD area after colloid administration was instituted (Tables 2 and 3). Additional evidence of regional myocardial ischemia comes from the significant reduction in the venous Po_2 draining the LAD segment (Table 3). This was accompanied by a significant increase in the carbon dioxide tension (Pco_2) and by a decrease in the pH (Table 3). The COD also was significantly reduced once volume was infused (Table 3).

In the four surgical control animals, none of the variables measured after the application of the constriction changed within a 2-h period (Table 4).

Discussion

Results indicate that in the acute open-chested pig model subjected to halothane anesthesia, colloid administration made early myocardial ischemia worse. This conclusion is based on (a) the reduction of the venous Po_2 and the increase in Pco_2 in the blood draining the myocardial segment supplied by the constricted coronary artery (14), (b) the increase in lactate production (15), and (c) the increase in the PSS (7). Our experimental results support previous findings, although our model is different from that of the other studies. In patients, the angina threshold was

Table 2. Segmental Function

	Control	Constriction	Volume
LAD segment			
Ees (mm Hg/mm)	28.70 ± 3.07	30.23 ± 4.00	23.68 ± 2.39
L_o (mm)	6.76 ± 0.39	6.89 ± 0.60	7.30 ± 0.68
Lmax (mm)	13.06 ± 0.49	13.02 ± 0.55	14.41 ± 0.59
dL%	23.73 ± 1.19	24.73 ± 1.46	23.84 ± 1.30
PSS (%)	9.62 ± 4.24	26.12 ± 5.81^a	36.22 ± 5.10^b
Work (mm Hg/mm)	234.11 ± 16.54	208.45 ± 23.27	251.49 ± 23.07
LX segment			
Ees (mm Hg/mm)	34.49 ± 4.59	44.51 ± 7.44	36.10 ± 4.23
L_o (mm)	8.06 ± 0.42	8.24 ± 0.69	8.41 ± 0.44
Lmax (mm)	13.53 ± 0.31	13.52 ± 0.32	14.40 ± 0.35
dL%	19.79 ± 1.28	20.20 ± 1.49	21.79 ± 1.40
PSS (%)	10.36 ± 4.13	4.59 ± 3.20	9.03 ± 3.33
Work (mm Hg/mm)	231.86 ± 42.86	188.23 ± 23.64	211.30 ± 28.91

Control, values recorded before application of stenosis; Constriction, values obtained after colloid administration was completed; Volume, values recorded after colloid administration; LAD, left anterior descending coronary artery; LX, left circumflex coronary artery; Ees, end-systolic pressure-length ratio; L_o, projected regional length at time left ventricular pressure = 0; Lmax, maximum regional length; dL%, systolic regional shortening normalized for Lmax; PSS, postsystolic shortening.

Values are mean ± SEM for seven animals.

$^a P < 0.05$ for comparison of control and constriction phases.

$^b P < 0.05$ for comparison of constriction and volume phases.

Table 3. Myocardial Oxygenation and Work of the Left Anterior Descending Coronary Artery Supply Region

	Control	Constriction	Volume
Pv_{O_2} (mm Hg)	41.60 ± 8.94	36.74 ± 9.37	17.34 ± 1.23^a
Sv_{O_2} (%)	31.36 ± 3.72	20.43 ± 0.97^b	17.43 ± 1.90
Pv_{CO_2} (mm Hg)	43.35 ± 3.15	50.85 ± 4.12^b	58.27 ± 9.23
pH_v	7.37 ± 0.01	7.34 ± 0.02	7.28 ± 0.01^a
Lactate extraction (%)	15.88 ± 2.38	−9.56 ± 5.32^b	−76.63 ± 19.19^a
COD	1.53 ± 0.08	1.34 ± 0.07^b	1.22 ± 0.03^a

Control, values recorded before application of stenosis; Constriction, values obtained after colloid administration was completed; Volume, values recorded after colloid administration; Pv_{O_2}, venous oxygen tension; Sv_{O_2}, venous blood hemoglobin saturation; Pv_{CO_2}, venous CO_2 tension; pH_v, pH in venous blood draining left anterior descending coronary artery region; Lactate extraction, arterial-venous lactate difference normalized for arterial lactate concentration expressed as percent; COD, coefficient of oxygen delivery.

Values are mean ± SEM for seven animals.

$^a P < 0.05$ for comparison of constriction and volume phases.

$^b P < 0.65$ for comparison of control and constriction phases.

reduced if the preload was augmented with low molecular dextran (4). In conscious dogs, reduction of the preload improved early diastolic dysfunction during reperfusion (16), and in patients with mild effort-related angina, it was demonstrated that myocardial wall motion abnormalities improved after an epidural anesthetic was given (17). This improvement in myocardial wall motion was associated with a significant decrease in LV end-diastolic volume; and if colloid administration was attempted, regional dysfunction became worse. The systolic function, judged from the static peak systolic pressure and end-systolic volume ratio, did not change throughout this study (17).

The mechanism by which colloid administration induces regional ischemia is not entirely clear. Global variables that could have affected myocardial oxygen demand did not change during this study. The heart rate remained constant; hence, the decrease in diastolic perfusion time to the left ventricle remained unaltered. Global and regional stroke work (both in the LAD and LX segments) did not change when colloid were administered to the animals; and as the myocardial oxygen consumption is related to stroke work (18), it seems unlikely that an increase in oxygen demand could explain the regional dysfunction that we observed.

Under ideal conditions, the subendocardium is more susceptible to ischemia because of the relative impairment of its vasodilatory reserve (19,20). During partial coronary constriction, resting blood flow to the myocardium is maintained by progressive distal vasodilatation (21). For instance, an 80% stenosis is associated with a 72-mm Hg decrease in pressure distal to the stenosis compared with the aortic (or proximal to the lesion) pressure (22), with the result that nutrient flow is shifted from the subendocar-

Table 4. Selected Variables Showing the Stability of the Model

	Control	Constriction	Constriction + 60 min	Constriction + 120 min
HR (beats/min)	111.00 ± 5.03	112.21 ± 4.10	113.21 ± 5.10	111.30 ± 4.21
MAP (mm Hg)	78.42 ± 6.10	72.22 ± 6.05	70.30 ± 4.93	71.45 ± 5.21
CO (mm Hg)	2.72 ± 0.22	2.71 ± 0.11	2.65 ± 0.37	2.72 ± 0.42
Ees LAD (mm Hg/mm)	29.67 ± 3.11	31.60 ± 4.62	30.70 ± 4.28	29.00 ± 4.21
L_o (mm)	7.01 ± 0.41	7.22 ± 0.64	7.11 ± 0.64	7.30 ± 0.62
dL%	24.44 ± 1.20	24.74 ± 1.60	24.20 ± 1.83	23.84 ± 2.91
PSS (%)	8.01 ± 4.20	23.22 ± 5.00[a]	24.11 ± 1.38	24.62 ± 2.01
Lactate extraction (%)	12.60 ± 4.00	−6.34 ± 4.11[a]	−8.93 ± 2.62	−5.34 ± 3.21
Pv_{O_2} (mm Hg)	40.01 ± 6.82	35.61 ± 9.44	34.21 ± 1.44	34.12 ± 3.60

Control, values recorded before application of the stenosis; Constriction, values obtained after colloid administration was completed; Constriction + 60 min, 60 min after application of constriction; Constriction + 120 min, 120 min after application of constriction; HR, heart rate; MAP, mean arterial pressure; CO, cardiac output; LAD, left arterior descending coronary artery; Ees, end-systolic pressure-length ratio; L_o, projected regional length at time left ventricular pressure = 0; dL%, systolic regional shortening normalized for Lmax; PSS, postsystolic shortening; Pv_{O_2}, venous O_2 tension.

Values are mean ± SEM for four animals.

[a] $P < 0.05$ for comparison of control and constriction phases.

dium to the subepicardium (23). Under these conditions, the perfusion pressure to the subendocardium is the difference between the pressure immediately distal to the lesion and the LVEDP. Experimental work has confirmed this concept. A study in dogs indicated that in the normal coronary artery, CBF is independent of LVEDP or LV end-diastolic volume. However, once distal vasodilatation occurred (caused by a flow-restrictive lesion), CBF was directly related to the perfusion pressure and an increase in LVEDP resulted in a decreased subendocardial flow (3).

However, Bellamy (24) has indicated that coronary blood flow was influenced by back pressure that exceeds coronary sinus or LV diastolic pressure. Aversano et al. (25) demonstrated that an increase in LVEDP did not affect CBF, provided the aortic diastolic pressure was maintained in excess of 65 mm Hg. However, if the aortic diastolic pressure was reduced to 30 mm Hg (which approximates the distal pressure in a 85% stenosis), raising the LVEDP resulted in a decrease of CBF. The authors concluded that the conduction decreased as preload increased and also indicated that the zero flow intercept ($P_{f\,=\,0}$) of the pressure-flow relationship increased as LVEDP was raised. It has also been demonstrated that halothane reduces the $P_{f\,=\,0}$ in dogs, thereby decreasing the level of CBF associated with ischemia; and the authors concluded that halothane induced an improved coronary vascular reserve (26). The initial concept that coronary perfusion pressure is the difference between aortic diastolic pressure and LVEDP should therefore be modified to account for $P_{f\,=\,0}$.

As there is an inverse relationship between early ventricular relaxation and CBF (27) and as CBF is maximal early in diastole (28), the change in early diastolic function (PSS in this study) observed during colloid administration could possibly explain the worsening of the regional ischemia. Various studies have indicated that ischemia results in poor diastolic relaxation (29–32). As PSS is an early marker of diastolic dysfunction caused by ischemia (7), it may well be that this diastolic dysfunction could have resulted in an increase in $P_{f\,=\,0}$ and could have reduced the already marginal coronary blood flow present after the constriction was applied. This resulted in a subminimal level of CBF and further deterioration of ischemia.

We are satisfied that the constriction we used was associated with a reduction in CBF to a point where early diastolic dysfunction occurred and metabolic markers for ischemia were present (11). Although the significance of lactate extraction has been questioned (33), the change from the lactate extraction to lactate production (in conjunction with the increase in PSS, decrease in venous P_{O_2}, and increase in venous P_{CO_2} [14]) does indicate a significant constriction. In a previous study, we have demonstrated that a significant increase in PSS and reduction in venous P_{O_2} were associated with a decrease in epicardial CBF from 81.48 ± 8.55 to 56.94 ± 7.12 $mL \cdot min^{-1} \cdot 100\ g^{-1}$. However, the lactate extraction was still within the normal range (10.54% ± 3.20%) (11). In the present study, the reduction in CBF was probably in excess of that reported in the previous study because we have demonstrated a significant change in lactate dynamics. However, in the absence of systolic dysfunction the increase in lactate production does differ significantly from that of the study of Waters et al. (10). They have documented lactate production when CBF was reduced to 48% ± 4% of control values, and in their study lactate production did correlate with systolic dysfunction. Waters et al. measured epicardial function, but one expects that at the time epicardial dysfunction is evident, endocardial dysfunction has already occurred. Except for some possible methodologic differences, we cannot explain the discrepancy between the two studies.

There are difficulties in the evaluation of Ees in the presence of severe ischemia (34), but the position of Ees in mild ischemia has not been systematically addressed. However, the regional shortening of the ischemic myocardium did not change, and this supports the contention that systolic dysfunction was absent.

In conclusion, we have indicated that colloid administration in the presence of an external coronary stenosis aggravates early regional ischemic dysfunction. However, we cannot explain the mechanisms with certainty because of our inability to measure CBF to the endocardium.

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Cardiac Surgery Causes Desensitization of the β-Adrenergic Receptor System of Human Lymphocytes

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Thirteen patients undergoing cardiac surgery were studied to examine whether β-adrenergic desensitization occurs in the perioperative period surrounding cardiac surgery, using peripheral blood lymphocytes as a model. Lymphocytes were isolated before induction of anesthesia (PRE) and on the morning of the first postoperative day (POST). Cyclic adenosine monophosphate (cAMP) production from the lymphocytes was assayed in the untreated (BASAL) state, and after treatment with 5 μM isoproterenol, 10 μM prostaglandin E_1, or 20 mM sodium fluoride with 10 μM $AlCl_3$ (NaF). All cAMP values are reported as picomoles per 10^6 cells, mean ± SEM. BASAL cAMP production did not change significantly between the PRE and POST samples (PRE, 1.2 ± 0.1; POST, 1.0 ± 0.1). Isoproterenol-stimulated cAMP was significantly lower postoperatively (PRE, 8.36 ± 0.9; POST, 5.1 ± 0.5; $P < 0.005$). Prostaglandin E_1-stimulated cAMP did not change (PRE, 21.7 ± 2.4; POST, 25.3 ± 2.5), and NaF-stimulated cAMP was increased postoperatively (PRE, 8.8 ± 1.6; POST, 14.3 ± 2.0; $P < 0.05$). These findings suggest that cardiac surgery and/or cardiopulmonary bypass results in significant desensitization of the β-adrenergic receptor/adenylate cyclase system of lymphocytes, which may parallel changes in the adrenergic response of other organ systems.

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Activation of the adrenergic system during the perioperative period has been a primary area of concern to anesthesiologists and intensivists over the past several decades. Studies have repeatedly demonstrated increases in plasma and urinary catecholamines during and after surgery. However, despite clinical impressions and suggestions that alterations in responsiveness of target tissues might occur (1,2), there has been little attention paid to possible perioperative changes in sensitivity to catecholamines and related pharmacologic agents. It is well known that chronic exposure to high concentrations of endogenous or exogenous catecholamines can result in a down-regulation of adrenergic receptors or desensitization of the tissue response to adrenergic stimulation (3–10). Acute exposure has also been shown to have the potential to result in desensitization of adrenergic response (11–16). Recently, several reports using the human lymphocyte as a model have suggested that alterations in β-adrenergic receptor characteristics may occur in surgical patients (17–20). As most of the cellular effects of β-adrenergic stimulation are mediated through the activation of adenylate cyclase and the formation of cyclic adenosine 3′,5′-monophosphate (cyclic AMP, cAMP), any physiologically or clinically relevant alteration in β-adrenergic receptor characteristics ought to involve a change in the ability of the cell to produce cAMP in response to an adrenergic stimulus. We have therefore examined whether surgery, including cardiopulmonary bypass, causes an alteration in the cAMP production of human lymphocytes.

Methods

Patients

The study was approved by the Institutional Review Board of the Columbia Presbyterian Medical Center. Informed consent was obtained from 13 patients scheduled to undergo cardiac surgery. These patients included nine undergoing coronary artery bypass surgery and four undergoing open heart procedures (valve replacement or atrial septal defect repair). The group consisted of eight men and five women, and the average age was 59 ± 4 yr (mean ± SEM). Clinical information regarding the subjects is detailed in Table 1.

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Table 1. Patient Data

Patient	Age (yr)	Sex	Operation	β-Block	Ca-block	Dig	Nitrate	Diuretic
1	49	F	MVR			X		X
2	62	M	CABG	X	X		X	
3	54	F	CABG		X		X	
4	28	F	ASD	X		X		X
5	85	M	CABG	X				
6	62	M	CABG				X	
7	58	F	MVR			X		
8	68	M	CABG		X			
9	48	M	AVR					
10	68	M	CABG	X	X		X	
11	56	M	CABG	X	X		X	
12	61	M	CABG					
13	70	M	CABG	X				

ASD, atrial septal defect repair; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; MVR, mitral valve replacement; β-block, X indicates patient receiving β-blockade therapy preoperatively (propranolol, metoprolol, or atenolol); Ca-block, patients receiving calcium-channel blocker therapy preoperatively (diltiazem, nifedipine, or verapamil); Dig, patients receiving digoxin preoperatively; Nitrate, patients receiving a nitrate preparation chronically; Diuretic, patients receiving diuretics (furosemide or hydrochlorthiazide).

Surgical Procedure

Patients were premedicated with 0.1 mg/kg of morphine and 0.2–0.4 mg of scopolamine IM, with 5–10 mg of diazepam administered orally 60–90 min before surgery. Induction and maintenance of anesthesia was accomplished primarily with fentanyl (50–120 μg/kg) and diazepam (25–50 mg) over the course of the operation, and ventilation was controlled and maintained with 100% O_2. Decisions regarding the details of anesthetic and operative management of the patients were left to the discretion of the attending anesthesiologists and surgeons. Volatile anesthetics, vasodilators, and vasopressors were used as needed. Before induction of anesthesia (PRE), a 40-mL blood sample was withdrawn from the radial arterial catheter; a second sample was drawn from the same arterial line on the morning of the first postoperative day (POST). At both time points an additional 5-mL sample was drawn for determination of plasma catecholamine concentrations. In preliminary experiments, seven cardiac surgical patients had blood sampled at the above two times and also from the cardiopulmonary bypass pump circuit 45–60 min after the initiation of bypass as rewarming was commencing. Another group of seven healthy, unmedicated volunteers not undergoing surgery had venous blood sampled on two consecutive days as part of the validation of the assays and procedures in the study. After collection, all blood samples were immediately placed in heparinized tubes and maintained at 4°C throughout the lymphocyte isolation in an attempt to prevent any alterations to the in vivo state of the adrenergic system of the lymphocytes (21).

Lymphocyte Isolation

Lymphocytes were isolated from whole blood according to a modification of the method of Boyum (22). The heparinized blood was diluted 1:1 with 0.9 N sodium chloride. Within 1 h of blood collection, mononuclear cells were isolated by centrifugation through a Ficoll-Hypaque gradient for 40 min at 400 *g*. The cell layer was suspended in phosphate-buffered saline (PBS: 10 mM Na_2HPO_4, 128 mM NaCl, 5.1 mM KCl, 1.2 mM $MgSO_4$, 5 mM glucose, adjusted to pH 7.4 with HCl) and washed three times by centrifugation at 100–200 *g*. The final pellet was suspended in 10 mL of PBS and stored at 4°C. Cells were counted by microscopy, with typical yields of $3\text{–}10 \times 10^7$ mononuclear cells from 40 mL of whole blood. These consisted of 80%–95% lymphocytes, ~10% monocytes, with >95% viability by trypan blue exclusion. Lymphocyte cAMP accumulation incubations were performed within 4 h of isolation, and preliminary experiments confirmed that cAMP production did not change after 4 h of storage at 4°C.

Cyclic Adenosine Monophosphate Accumulation

Lymphocytes were incubated for 12 min at 37°C (10^6 cells in 1 mL of PBS, pH 7.4) in the presence of 0.1 mM 3-isobutyl-1-methylxanthine to inhibit phosphodiesterase activity. Cyclic AMP production was assayed in the untreated (BASAL) state and in the presence of the β-adrenergic agonist isoproterenol (5 μM), prostaglandin E_1 (PGE_1, 10 μM), and 20 mM sodium fluoride with 10 μM $AlCl_3$ (NaF). All reagents were added in 10 μL of PBS, with the BASAL receiving 10 μL of PBS. Preliminary experiments demonstrated that the above concentrations of isoproterenol, PGE_1, and NaF resulted in maximal stimulation of cAMP. The incubations were terminated by placing the tubes in boiling water for 5 min followed by centrifugation at 3000 *g* for 15 min at 4°C. The supernatant was removed and frozen at −70°C until determination of cAMP by radioimmunoassay (Biomedical Technologies, Stoughton, Mass.).

Plasma Catecholamine Concentrations

The concentrations of epinephrine and norepinephrine were determined by high-performance liquid chromatography with electrochemical detection by established methods (23). Complete preoperative and postoperative data were obtained for 10 of the 13 patients. The lower limit for detection was approximately 75 pg/mL. Epinephrine levels were frequently below this level preoperatively (and occasionally postoperatively); a value of 75 pg/mL has been assigned to these samples for purposes of statistical analysis.

Statistical Analysis

Unless otherwise designated, data are reported as mean ± SEM. Data on lymphocyte cAMP production and plasma catecholamine concentrations were compared at the two time points (PRE and POST) by two-tail paired *t*-test, so that each patient's preoperative status served as his/her own control. Statistical significance was confirmed at the $P < 0.05$ level. Perioperative increases in plasma norepinephrine and epinephrine were compared with the decrease in isoproterenol-stimulated cAMP in individual patients by linear regression.

Results

Lymphocyte Cyclic Adenosine Monophosphate

As indicated in Figure 1, basal cAMP production did not change from the PRE to POST time points (1.2 ± 0.5 vs 1.0 ± 0.1 pmol/10^6 cells, respectively). At both time points, isoproterenol significantly stimulated cAMP production; however, isoproterenol-stimulated cAMP production was significantly lower in lymphocytes on postoperative day 1 compared with the preoperative samples. Isoproterenol-stimulated cAMP decreased 40% (PRE, 8.4 ± 0.9; POST, 5.1 ± 0.5 pmol/10^6 cells; $P < 0.005$). In contrast, PGE_1-stimulated cAMP did not change significantly (PRE, 21.7 ± 2.4; POST, 25.3 ± 2.5 pmol/10^6 cells). Cyclic AMP in lymphocytes treated with NaF increased significantly (PRE, 8.8 ± 1.6; POST, 14.3 ± 2.0 pmol/10^6 cells; $P < 0.05$). The individual patient data are shown graphically in Figure 2. In the seven nonsurgical volunteers, BASAL and isoproterenol-stimulated cAMP were not different on the two sampling days (data not shown). Prostaglandin E_1

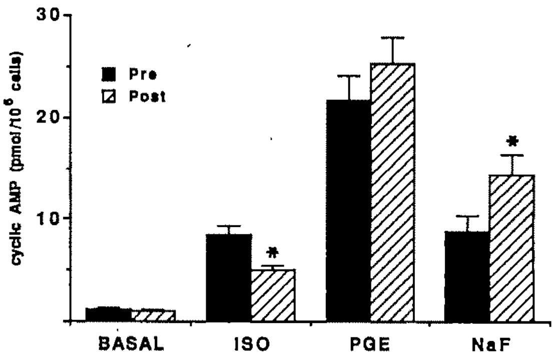

Figure 1. Lymphocyte cAMP production. Pre, lymphocytes isolated from blood sample taken preinduction; Post, lymphocytes from the morning of the first postoperative day after cardiac surgery. BASAL, saline-treated lymphocytes; ISO, 50 μM isoproterenol; PGE, 10 μM prostaglandin E_1; NaF, 20 mM sodium fluoride with 10 μM aluminum chloride. *Significantly different from preoperative value, $P < 0.05$.

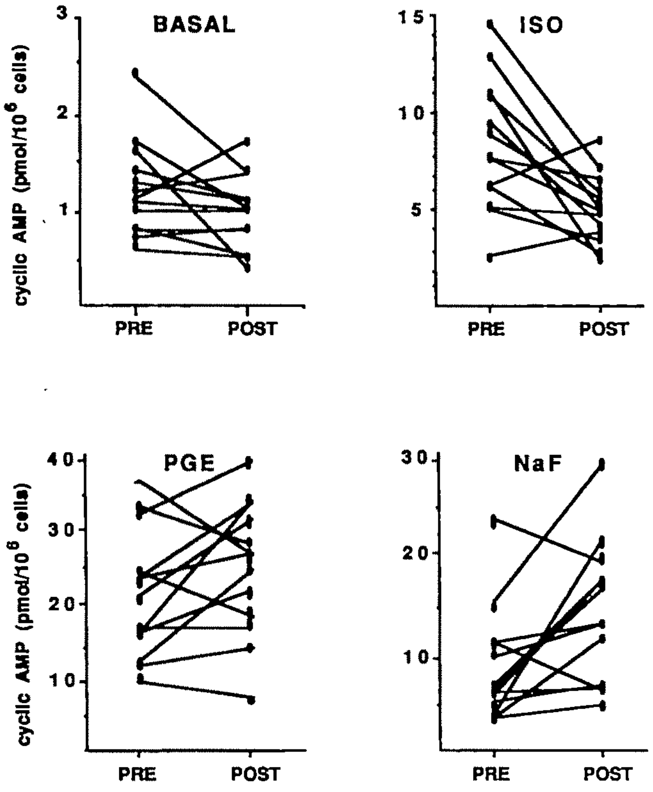

Figure 2. Lymphocyte cAMP production from individual patients. *Each line* connects two points that indicate lymphocyte cAMP production from a single patient in response to the indicated agent. PRE, lymphocytes isolated from blood sample taken preinduction; POST, lymphocytes from the morning of the first postoperative day after cardiac surgery.

Table 2. Plasma Catecholamine Concentrations

	Preoperative	Postoperative
Epinephrine (pg/mL)	183 ± 59	555 ± 170
Norepinephrine (pg/mL)	722 ± 94	1766 ± 390

Values are mean ± SEM (n = 22).

and NaF treatments were not performed on lymphocytes from these patients. There were no significant differences between the patients undergoing valve replacement and those undergoing coronary artery bypass surgery.

Plasma Catecholamine Concentrations

Mean plasma epinephrine and norepinephrine were increased postoperatively (Table 2). There was no correlation of postoperative catecholamine concentrations or relative perioperative increases with the decrease seen in isoproterenol-stimulated cAMP production in individual patients.

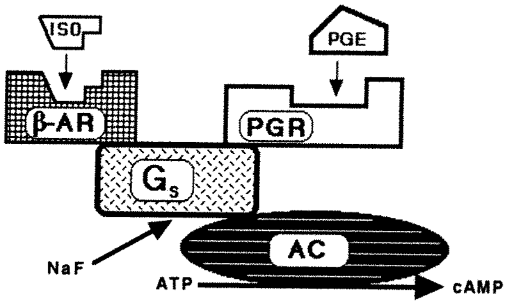

Figure 3. Receptor/adenylate cyclase complex. Location of action of various pharmacologic agents on lymphocyte adenylate cyclase. ISO, isoproterenol; PGE, prostaglandin E_1; NaF, sodium fluoride; ATP, adenosine triphosphate; cAMP, cyclic adenosine 3′,5′-monophosphate; β-AR, β-adrenergic receptor; PGR, prostaglandin receptor; G_s, stimulatory guanine-nucleotide binding protein; AC, adenylate cyclase.

Discussion

The β-adrenergic receptor has been widely studied as a model for the incidence and mechanism of receptor down-regulation and desensitization (8). Agonist binding to the β-receptor causes the receptor to interact with and activate the stimulatory guanine nucleotide binding protein (G_s), which activates adenylate cyclase. Adenylate cyclase catalyzes the conversion of adenosine triphosphate to cAMP. Cyclic AMP activates the cAMP-dependent protein kinase, resulting in phosphorylation of particular proteins and specific actions that depend on the cell and tissue type, e.g., inotropy and chronotropy in myocardial tissue, relaxation in vascular smooth muscle, or lipolysis in adipose tissue. Alterations in adrenergic response may result from changes at any level of this cascade.

There have been a few studies of β-adrenergic receptor regulation in the perioperative period. Eandi et al. (17) reported a 40% decrease in the number of β-receptors on lymphocytes from patients undergoing minor surgery when measured 24 h postoperatively, which returned to normal by 36 h postoperatively. Mantz et al. (18) reported that the affinity of lymphocyte β-adrenergic receptors for isoproterenol was decreased postoperatively in some patients undergoing coronary artery bypass surgery, particularly in those patients with high intraoperative plasma catecholamine concentrations, whereas receptor density on the cell surface was slightly increased. Another study from the same group reported a modest decrease (~20%) in receptor affinity for isoproterenol after noncardiac surgery in the subset of patients with intraoperative increases in catecholamines (19). In a study involving a different receptor system, α_2-adrenergic receptors on platelets were shown not to be down-regulated by cardiopulmonary bypass (24). However, α_2-receptors appear somewhat resistant to down-regulation relative to the β-receptors, which have been studied more extensively (25). None of these perioperative studies examined any changes in cellular physiology that might have resulted from the changes in β-receptor characteristics, such as adenylate cyclase activity or availability and activation of the G_s protein.

Our data indicate a postoperative decrease in the maximal cellular response to isoproterenol. Prostaglandin E_1 stimulates cAMP formation via the same G-protein (G_s) as β-adrenergic activation but does so by occupation and activation of a different surface receptor. Sodium fluoride acts at another site on the G-protein or on adenylate cyclase itself (Figure 3). In the cells studied, response to prostaglandin E_1 was maintained perioperatively. This may imply that the "molecular defect" or alteration that occurs in the lymphocyte receptor-cyclase complex perioperatively is at the level of the β-receptor itself or involves the ability of the receptor to interact with and activate the G-protein, a phenomenon referred to as uncoupling. The retained or increased cAMP production in response to sodium fluoride, which activates the cascade directly at the G_s or cyclase level, further supports this interpretation, as it suggests that the distal receptor-effector complex remains relatively intact. It is tempting to conclude that the perioperative activation of the sympathetic nervous system, with consequent increased concentrations of plasma epinephrine and norepinephrine caused a "reflex" desensitization of the lymphocytes' response to such activation. If a similar process were to occur, for example, in the myocardium, one would predict a relative decrease in contractility and heart rate with a blunted response to endogenous or exogenous catecholamines and related agents. Indeed, Marty et al. (19) reported that those patients with reduced lymphocyte β-receptor affinity for isoproterenol had attenuated heart rate responses to adrenergic stimulation postoperatively. It should be noted, however, that we could not demonstrate a correlation between the degree of increase in plasma catecholamines and the degree of decrease in isoproterenol-stimulated cAMP production in lymphocytes. This may be partially explained by the heterogeneity and relatively small sample size of the population studied, or it could imply that stimuli other than plasma catecholamines may be responsible. We only measured catecholamine concentrations at two time points, and this may not be sufficient to characterize the "stress response" to surgery. More frequent sampling of serum catecholamines might have clarified this issue. If desensitization of myocardial and other β-receptors is a common occurrence perioperatively, especially if it is related to or caused by activation of the sympathetic nervous system, it could have significant implications for strategies of clinical management. For example, it would serve as a further argument in favor of clinical maneuvers and/or pharmacologic agents aimed at eliminating or blunting the stress response to surgery.

There are several reasons to be cautious about drawing such conclusions from our results. The human lymphocyte has been widely used for the study of β-adrenergic receptor mediated phenomena because of the accessibility of the cells. However, using lymphocyte β-receptors as markers for β-receptors on other organs can be problematic. Lymphocytes possess β_2-adrenergic receptors that have been shown to be accurate in reflecting changes in β_2-receptors in other organs but less useful for reflecting alterations in properties of β_1-adrenergic receptors (26). The heart possesses both β_1- and β_2-receptors, and there is evidence that they are differentially regulated (27,28). In addition, all the study patients underwent cardiac operations that involved cardiopulmonary bypass, so circulating lymphocytes were exposed to the roller pump, oxygenator, and other aspects of the cardiopulmonary bypass machine in a much more direct way than other organ systems. It is possible that such exposure could cause nonspecific alterations or cell damage that could be misinterpreted as desensitization or receptor down-regulation. However, lymphocytes isolated near the end of the bypass run from seven patients did not demonstrate the decrease in cAMP production seen in cells isolated on the first postoperative day, supporting the interpretation that the decreases in cAMP response were due to adrenergic hyperstimulation over a period of time, rather than simply "pump trauma." Further, the retained cAMP response to isoproterenol (fivefold increase over BASAL postoperatively) and the ability of PGE_1 and NaF to cause the same or increased formation of cAMP postoperatively argue against significant cell damage.

The patients studied in this investigation received a variety of medications preoperatively that could have affected the results, although no obvious correlation of lymphocyte response with medical treatment was seen. Chronic β-blockade may cause an "up-regulation" of receptor number and cAMP response of cells, and one might speculate that these patients would be more susceptible to subsequent desensitization when the blockade is removed and the patient is exposed to significant adrenergic stimulation during the perioperative period. Calcium channel blockers may interact with the β-adrenergic system, and there is evidence that calcium channel blockers may prevent desensitization in lymphocytes under certain conditions (29). The data reported here do not allow for any detailed analysis of these factors.

A potentially more significant issue regarding this type of study on lymphocytes is that it has recently been demonstrated that some apparent acute and subacute alterations in lymphocyte receptor properties and cAMP production in a variety of settings are actually due to changes in the proportions of the subpopulations of circulating lymphocytes (30–32). The various subpopulations of lymphocytes have different numbers of β-receptors and different cAMP responses to agonists (31). Changes in circulating lymphocyte subpopulations have been reported to occur during the perioperative period of cardiac surgery (33–35). It is possible that changes in the ratios of the various cell types could explain all or part of the cAMP production alterations we report here. However, if one examines the data from the studies of Tonnesen et al. (33) on lymphocyte subpopulation alterations and the information from Maisel et al. (31) on cAMP responses of the various subpopulations, the prediction would be a slight increase in isoproterenol-stimulated cAMP from lymphocytes on the first postoperative day rather than the significant decrease reported here. Preliminary data on lymphocyte subpopulation alterations with cardiac surgery at our institution suggest similar changes to those reported by Tonnesen et al. (data not shown); thus, it appears unlikely that the changes in cAMP production reported in this study could be attributed exclusively to an alteration in lymphocyte subpopulation ratios. Some of the above limitations will be addressed in a follow-up study of a more homogeneous patient population undergoing coronary artery bypass surgery. This will include assessments of lymphocyte subpopulations along with receptor density and binding affinity alterations in addition to cAMP production in response to a variety of pharmacologic agents. Animal studies could allow examination of receptor changes in other organs (e.g., heart, vasculature, adipose tissue) that would complement human lymphocyte studies. Finally, it is important to note that alterations in cAMP production in vitro are not always reflected in cellular or organ physiology. In some systems a maximal cellular response may be elicited by a small fraction of the amount of cAMP produced by a cell, and thus a decrease in the ability to generate cAMP may or may not have physiologic significance. This limitation in extrapolating from in vitro to in vivo is perhaps even more true of studies that only examine surface receptor binding properties, owing to the frequent presence of "spare" receptors, such that only a portion of the total number of receptors need to be occupied to generate a maximal cellular response. Thus, any conclusions of this or other studies of receptor and second messenger function in the perioperative period will be strengthened by correlation with clinical and physiologic variables.

In conclusion, we have demonstrated that surgery including cardiopulmonary bypass results in a significant decrease in isoproterenol-stimulated cAMP production in human lymphocytes without a change in PGE_1-stimulated cAMP, suggesting an alteration in the β-receptor/adenylate cyclase complex at the level of the receptor or of receptor coupling to the signal transducing protein G_s.

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Influence of Five Different Priming Solutions on Platelet Function in Patients Undergoing Cardiac Surgery

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The ideal choice of a priming solution of the cardiopulmonary bypass (CPB) and its influence on the hemostatic system are not clear. Addition of albumin was reported to inhibit platelet damaging by blood-surface interactions ("coating"). To explore this possibility in 60 consecutive male patients undergoing elective aortocoronary bypass grafting, five different priming solutions were randomly used: (1) 1000 mL of 5% dextrose + 1000 mL of Ringer's solution (RS) + 250 mL of 5% human albumin (HA); (2) 1850 mL of RS + 400 mL of 20% HA; (3) 1750 mL of RS + 500 mL of 10% low molecular weight hydroxyethyl starch (molecular weight average: 200,000; molar substitution ratio: 0.5); (4) 1750 mL of RS + 500 mL of 3.5% gelatin; (5) 2250 mL of RS. Platelet function was studied by aggregometry (= turbidometric technique; 1.0 and 2.0 μmol/L of adenosine diphosphate (ADP), 4 μL/mL of collagen, 25 μmol/L of epinephrine) before, during, and after CPB until the first postoperative day. Blood loss and need for homologous blood was not different between the groups. During CPB, maximum platelet aggregation induced by ADP was least compromised in group 1 and group 4. At the end of the operation ADP-induced aggregation increased in group 1 (+27%), whereas aggregation was decreased in the other priming solution groups. A significant increase in maximum aggregation was found in group 1 even on the first postoperative day (+132% ± 16%). Collagen-induced aggregation was also least compromised in group 1. Epinephrine-induced platelet aggregation did not change and was similar for all groups. Maximum gradient of aggregation was influenced in an identical way as maximum aggregation. We concluded that a priming solution consisting of dextrose, RS, and 250 mL of 5% HA was overall most effective in preserving platelet function. Addition of gelatin was not as effective for this purpose. Moreover, other aspects (e.g., material of the CPB, flow, temperature) appear to be more important with regard to platelet function than the choice of a prime solution.

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The solution used to prime the cardiopulmonary bypass (CPB) varies widely. There is still no consensus in the ideal priming solution, particularly with regard to hemostasis (1). During CPB, blood is continuously exposed to the nonendothelial, synthetic surfaces of the extracorporeal oxygenation circuit (2,3). Platelet adhesion and protein denaturation are possible sequelae of this blood/surface contact. Denaturated protein results in cellular aggregation, sludging, and microthrombosis. Denaturation of red cell membranes induces a release of adenosine diphosphate (ADP), which leads to aggregation (4). The vicious cycle is continued as aggregated platelets release more ADP, promoting further platelet aggregation (4). Preexposure of synthetic surfaces to albumin ("coating") decreases the affinity of platelets to synthetic surfaces (5,6): platelet granule release would be reduced and morphologic integrity of the platelets would be preserved when using surface-absorbed albumin (7). Impairment in platelet function secondary to CPB is one of the most important reasons for enhanced and prolonged bleeding in open heart surgery (8). Approximately 10%–20% of patients undergoing cardiac surgery procedures exhibit inadequate hemostasis varying in its duration and severity. These patients often require treatment with homologous blood or blood products (9). Surgical reexploration is required in approximately 3% of these patients (8). This study was performed to investigate whether different priming of the extracorporeal circuit influences platelet function and postbypass bleeding in cardiac surgery patients.

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Methods

Sixty male patients scheduled for elective aortocoronary bypass grafting were included in this study. According to the protocol of the human ethic study committee of the hospital, all patients gave informed consent to participate in the study. Exclusion criteria were preoperative coagulation disorders, concomitant valvular diseases, and medication with aspirin or other cyclooxygenase inhibitors within the last 10 days.

Preoperatively, the patients were allocated prospectively at random to one of the following groups with different priming of the heart lung machine:

1 (*n* = 12). The extracorporeal circuit was primed with 1000 mL of Ringer's solution (RS), 1000 mL of 5% dextrose, and 250 mL of 5% human albumin (HA). This has been our priming for years (standard priming).
2 (*n* = 12). Priming solution consisted of 1850 mL of RS and 400 mL of 20% HA (albumin priming).
3 (*n* = 12). Priming solution consisted of 1750 mL of RS and 500 mL of low molecular weight hydroxyethyl starch solution (LMW-HES) (10% HES, molecular weight average [MW]: 200,000; molar substitution ratio: 0.5) (HES priming).
4 (*n* = 12). Priming solution consisted of 500 mL of gelatin (3.5%) and 1750 mL of RS (gelatin priming).
5 (*n* = 12). The heart-lung machine was primed only with 2250 mL of RS (crystalloid priming).

Induction and maintenance of anesthesia were performed by the intravenous administration of weight-related doses of fentanyl, pancuronium, and midazolam. Anesthetic procedure was standardized and comparable for all patients.

Bovine lung heparin (300 IU/kg) was injected 5 min before the start of CPB, which was carried out by using a nonpulsatile pump and membrane oxygenators (Sorin 41, Sorin, Torino, Italy). Identical polyvinylchloride and silicone tubing was used in all patients. Priming was chosen according to the randomized grouping list. A flow of 2.4 $L \cdot min^{-1} \cdot m^2$ was maintained within the entire bypass period (lowest rectal temperature = 33.8 ± 0.5°C). Blood was returned to the circuit using a two-stage cannula (monoatrial-cannulation technique). This technique implies that all fluids (cardioplegic solution, suction, cooling) are returned to the extracorporeal circuit. One thousand milliliters of cardioplegic solution (based on low sodium [15 mmol/L] and absence of calcium, contains mannitol [20 mmol/L], is buffered with histidine [180 mmol/L], and was infused for myocardial preservation. Within 20 min after the start of CPB, the blood of the circuit was concentrated using a hemofiltration device (HF-80, Fresenius, Bad Homburg, Germany) with the aim to adjust hemoglobin between 8 and 10 g/dL. Ringer's solution was added when necessary in the further course of the bypass period to maintain adequate volume of the extracorporeal circuit. Packed red cells were infused when hemoglobin was less than 7.5 g/dL. As much pump blood as necessary to keep pulmonary capillary wedge pressure between 10 and 12 mm Hg was infused during weaning from bypass. After separation from CPB, the residual blood of the circuit was salvaged by the hemofiltration device, and the autologous blood was retransfused until the end of the operation. Protamine sulfate was given in the same dosage as the initially administered heparin dose to antagonize heparin effects.

Platelet aggregation was studied from arterial blood samples using the turbidometric method (10) and a double-channel APACT-aggregometer (Labor, Ahrensburg, Germany). Platelet count was adjusted to 150,000 platelets/mm^3 before aggregometry. Aggregation was induced by ADP (1.0 and 2.0 μmol/L), collagen (4 μg/mL), epinephrine (25 μmol/L), and NaCl (control). *Maximal platelet aggregation* was defined as the maximum increase in light transmission after addition of the aggregation agent (read as percentage increase). *Maximum gradient of platelet aggregation* was defined as the maximum increase per minute (read as percentage increase per minute).

The measurements were performed after induction of anesthesia (baseline values), 20 min after onset of CPB (after hemoconcentration by hemofiltration technique), after separation from CPB (before infusion of protamine), at the end of operation (45 min after CPB), 5 h after the end of CPB, and on the morning of the first postoperative day. Hemoglobin, hematocrit, platelet count, activated clotting time and thromboelastogram (before and after operation) were also measured.

In the postoperative period, 5% albumin was infused to maintain stable hemodynamics (when pulmonary capillary wedge pressure was less than 7 mm Hg and cardiac index was less than 2.30 $L \cdot min^{-1} \cdot m^2$), and packed red cells were given when hemoglobin concentration was below 9 g/dL. All volume therapy was indicated by anesthesiologists not involved in the study and blinded to the priming solution. Blood loss from the chest tube drainages and use of homologous blood were also documented. Shed mediastinal blood was not retransfused during the postoperative period.

Mean values ± standard deviation (SD) were calculated for each parameter. One- and two-factorial analyses of variance (including multitesting analysis of variance) followed by the Scheffe test were used for statistical interpretation. In addition, percentage changes were calculated for aggregation variables.

Table 1. Comparison of Clinical Data With Each Priming Solution

	Priming solution				
	Standard	Albumin	HES	Gelatin	Crystalloid
Age (yr)	60.3 ± 5.7	62.6 ± 10.5	63.9 ± 9.2	61.4 ± 8.8	59.8 ± 11.1
Weight (kg)	77.1 ± 6.3	75.5 ± 13.7	76.5 ± 9.0	79.2 ± 14.2	73.9 ± 10.3
LVEF (%)	68.2 ± 15.9	68.0 ± 15.3	71.0 ± 14.4	68.8 ± 13.8	66.5 ± 11.2
LVEDP (mm Hg)	8.5 ± 4.0	11.8 ± 5.3	10.0 ± 6.0	9.6 ± 3.5	11.7 ± 5.0
Period of CPB (min)	85.6 ± 20.1	83.3 ± 10.7	82.9 ± 24.1	82.9 ± 20.5	79.9 ± 17.9
Ischemia (min)	53.6 ± 16.9	54.6 ± 11.43	50.0 ± 17.3	52.6 ± 18.4	47.7 ± 11.3
Fluid balance during CPB (mL)	+210 ± 400	+70 ± 410	+20 ± 390	+300 ± 490	+690 ± 600*
Blood loss (mL)					
Operation day	180 ± 70	270 ± 120	250 ± 150	290 ± 160	240 ± 90
First postoperative day	440 ± 100	530 ± 240	550 ± 210	560 ± 220	530 ± 150
Homologous blood	0	1 patient 1 unit	1 patient 1 unit	2 patients 2 units	0

CPB, cardiopulmonary bypass; HES, hydroxyethyl starch; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end-diastolic pressure.
Values are mean ± SD.
*$P < 0.05$ vs. other groups.

Table 2. Platelet Counts and Hemoglobin Concentrations With Each Priming Solution

Variable	Group	Baseline	During CPB	5 min after CPB	45 min after CPB	5 h after CPB	1st po day
Platelets (10^9/L)	Standard	172 ± 44	152 ± 33	156 ± 40	153 ± 45	170 ± 33	165 ± 32
	Albumin	200 ± 35	166 ± 33	153 ± 31	151 ± 25	149 ± 22	157 ± 26
	HES	189 ± 43	143 ± 41	156 ± 43	176 ± 39	192 ± 47	182 ± 30
	Gelatin	216 ± 56	175 ± 62	189 ± 66	188 ± 78	180 ± 76	190 ± 59
	Crystalloid	171 ± 57	137 ± 53	193 ± 66	188 ± 78	180 ± 76	198 ± 59
Hgb (g/dL)	Standard	12.3 ± 1.4	9.1 ± 0.6	9.8 ± 0.6	11.1 ± 0.6	12.5 ± 1.4	12.3 ± 1.6
	Albumin	12.2 ± 1.3	8.0 ± 1.0	9.0 ± 0.9	10.9 ± 1.0	12.0 ± 1.1	12.1 ± 1.0
	HES	12.9 ± 1.5	8.7 ± 0.7	9.4 ± 0.8	11.3 ± 0.9	11.9 ± 1.0	11.5 ± 1.0
	Gelatin	12.6 ± 0.9	8.9 ± 1.0	9.9 ± 1.2	11.8 ± 1.6	12.9 ± 0.9	11.9 ± 0.8
	Crystalloid	12.7 ± 1.1	8.1 ± 2.3	9.9 ± 1.0	12.0 ± 0.8	12.9 ± 1.5	11.6 ± 1.5

CPB, cardiopulmonary bypass; Hgb, hemoglobin; HES, hydroxyethyl starch; po, postoperative.
Values are mean ± SD.

H-tests (Kruskall-Wallis) were additionally used to test percentage changes. P values <0.05 were considered significant.

Results

Biometric and CPB data were without differences between the groups (Table 1). Blood loss and use of homologous blood were also comparable for the groups: two patients given a priming solution to which gelatin was added needed 2 U of packed red cells postoperatively, and 1 U of packed red cells was given in the albumin and HES groups (Table 1).

The degree of hemodilution (hemoglobin) and platelet count (Table 2) did not differ among the groups within the entire investigation period. Platelet aggregation, however, did differ between the five groups (Figures 1–4). During CPB, aggregation induced by 1.0 μmol/L of ADP increased significantly in group 1 (standard: +84% ± 12%) and group 4 (gelatin: +78% ± 13%). In the postbypass period, aggregation remained elevated in group 1, which could be demonstrated even on the first postoperative day (+132% ± 16%). Aggregation in the other groups remained almost unchanged or even decreased at the end of the operation. Platelet aggregation induced by 2.0 μmol/L of ADP reacted similarly: the increase in aggregation was highest in group 1 (+48% ± 12% during CPB) and remained elevated until the end of the investigation (+65% ± 12% on the first postoperative day). In the other groups, aggregation was significantly less increased or even decreased (at the end of the operation). Collagen-induced aggregation increased only in group 1 (+95% ± 15% after weaning from CPB; +148% ± 29% on the first postoperative day). Epinephrine-induced aggregation (Figure 4) was not significantly different between the groups within the entire investigation period. The maximum gradient of aggregation reacted similarly to the maximum aggregation values.

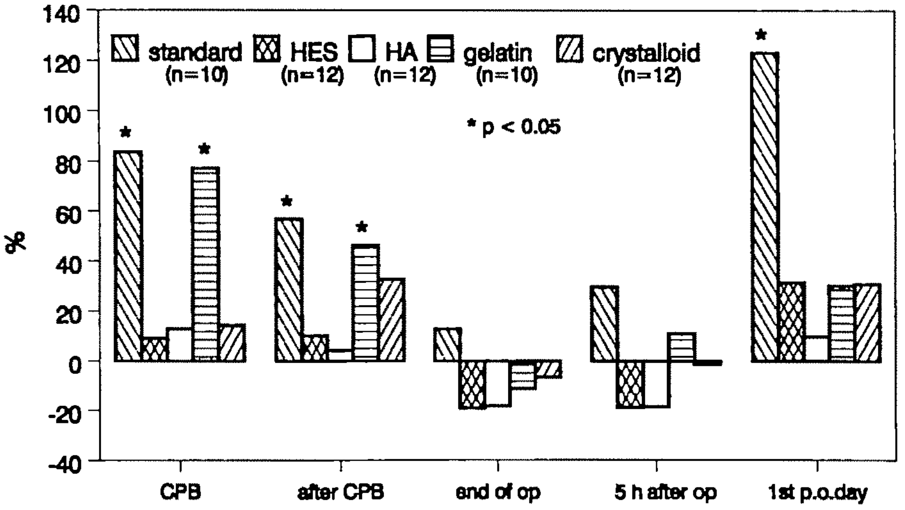

Figure 1. Changes in maximum aggregation (%) induced by 1.0 μmol/L of ADP in the different groups compared with preoperative control. CPB, cardiopulmonary bypass; op, operation; p.o., postoperative; HES, hydroxyethyl starch; HA, human albumin; *$P < 0.05$, different from the other groups.

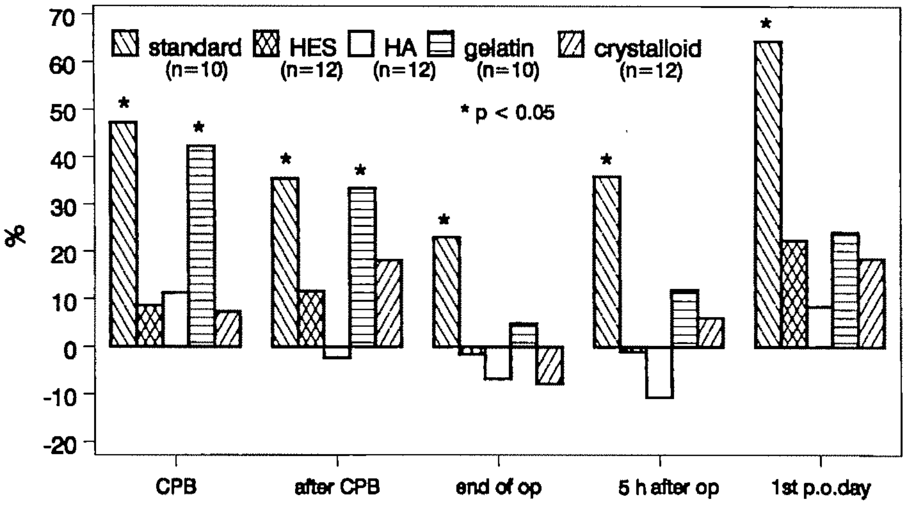

Figure 2. Changes in maximum aggregation (%) induced by 2.0 μmol/L of ADP in the different groups compared with preoperative control. CPB, cardiopulmonary bypass; op, operation; p.o., postoperative; *$P < 0.05$, different from the other groups.

None of the patients required further surgery because of postoperative bleeding.

Discussion

Cardiopulmonary bypass induces a variety of different alterations in coagulation. Acquired platelet dysfunction seems to be a very important effect of the interaction of foreign materials with blood (3,11). Perhaps heparin, while blocking clot formation, cannot prevent platelet aggregation and activation of the enzymatic cascades related to factor XIII (12). As there does not exist completely blood-compatible synthetic surfaces, priming of the CPB equipment is thought to modify the negative blood-surface interactions (6).

In general, the behavior of platelets during CPB can be divided into three different categories: (a) adherence, (b) aggregation, and (c) granule secretion (5,13–16). Platelet adhesion at the foreign surface is the initial step of platelet alteration. Platelet-to-surface and platelet-to-platelet interactions induce platelet aggregation. Fibrinogen binding and glycoprotein are necessary for platelet aggregation (receptor-dependent). When platelet activation progresses, α- and dense granule secretion occurs, by which membrane receptors of the platelets are altered and aggregation is changed. A reduction in the fibrinogen binding sites is probably an important

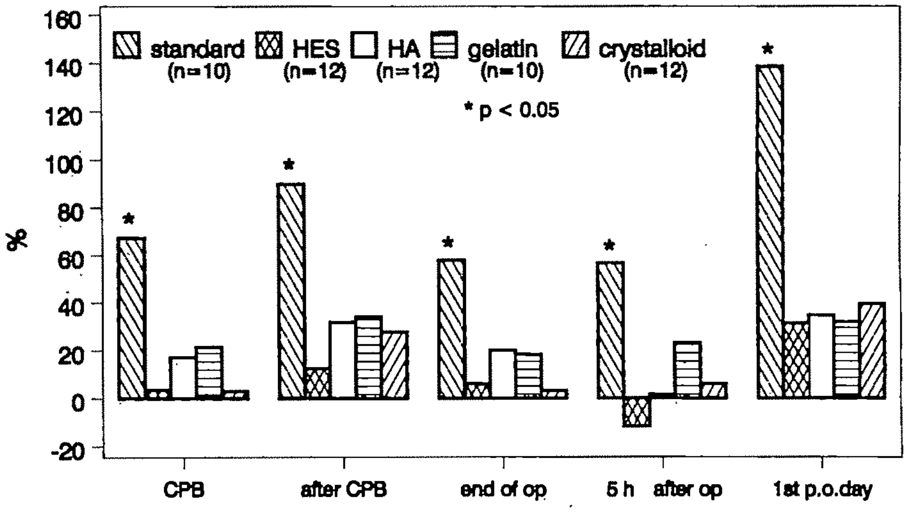

Figure 3. Changes in maximum aggregation (%) induced by 4 μg/L of collagen in the different groups compared with preoperative control. CPB, cardiopulmonary bypass; op, operation; p.o., postoperative; $^*P < 0.05$, different from the other groups.

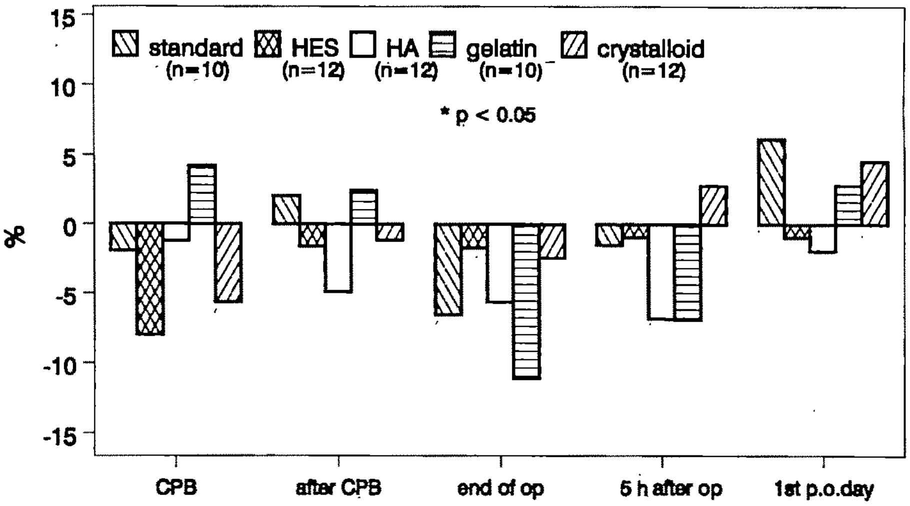

Figure 4. Changes in maximum aggregation (%) induced by 25 μmol/L of epinephrine in the different groups compared with preoperative control. CPB, cardiopulmonary bypass; op, operation; p.o., postoperative; $^*P < 0.05$, different from the other groups.

reason for deterioration in platelet function. The exact pathological mechanism of the platelet dysfunction is still not defined precisely (5).

The benefit of adding albumin to the priming solution is based on the assumption that albumin may form an almost nonthrombogenic surface layer (6). However, whether this can be achieved by precirculation of priming solutions containing albumin or synthetic colloid remains unclear. Packham et al. (17) investigated the effects of surface coating with albumin on platelet functions in vitro: surfaces coated with albumin resulted in less adherence and subsequent release of platelet constituents.

Hydroxyethyl starch is a synthetic colloid that may replace much more expensive albumin as an additive to the priming solution. Saunders et al. (18) demonstrated that the addition of HES to priming solutions resulted in less abnormal platelet aggregation than did the addition of albumin and suggested that HES is a safe additive to priming solutions. By contrast, Palanzo et al. (19) found a more pronounced decrease in platelet count in patients with HES-primed CPB in comparison with patients with albumin-primed CPB (300 mL of 20% HA). Andrew (20) found no differences between HES and albumin priming when looking at platelet survival and fibrinogen changes. In an interinstitutional study, Mishler et al. (21) studied 85 patients undergoing cardiac surgery. They demonstrated no significant differences in clotting and bleeding time, thromboelastogram, and blood loss. High molecular weight HES (HMW-HES: MW 450,000) was used in all these studies. The HMW-

HES solution, however, is known to impair coagulation much more than LMW-HES preparations (MW 200,000). Thus, we decided to add LMW-HES to the priming solution because the coagulation system is expected to be significantly less deteriorated by this HES than by other synthetic colloids (i.e., HMW-HES or dextran) (22).

Gelatin is another synthetic colloid used either for intravascular volume replacement or priming solution additive. Bonser et al. (23) found a reduction in complement activation when adding polygeline to the priming solution. As complement activation might result in deterioration of various organ functions, this was suggested as an inexpensive method to reduce morbidity after CPB.

Crystalloid priming represents the least expensive way of priming. Comparing a priming solution containing dextran or not (crystalloid priming), Kongsgaard et al. (24) found no intergroup differences with regard to the kallikrein-kinin, fibrinolytic, and coagulation systems. Dextran, however, is known to possess the most negative effects on coagulation of all synthetic colloids. Marelli et al. (25) recently reported on a prospective study in 100 cardiac surgery patients some of whom had albumin added to the priming solution of the extracorporal circuit. They found few differences in patient outcome and doubted the value of adding albumin to the priming solution. Costs are increased markedly and the overall consequences are ambiguous. One major finding from our study was that postbypass bleeding was comparable for all priming solution groups. There were also no significant differences in need for homologous blood.

Several studies reported on a reduction in aggregation variables secondary to CPB that was explained by a platelet dysfunction (5,14,15). The overall best effect on platelet aggregability was observed in those patients in whom our standard priming solution was used (group 1). Addition of gelatin resulted in an increased platelet activation (increase in maximum aggregation and maximum gradient of aggregation). Perhaps platelets in these groups were less damaged and their capability to react to inductors such as ADP and collagen remained less compromised than in the other patients. Mere crystalloid priming, addition of HES, or even addition of high-dose albumin have had significantly less beneficial effects on platelet function.

A comparison of our results with other studies is difficult because of widely varying study conditions: different oxygenators and suction technique, varying temperatures and flow profile, different blood conservation techniques—all may influence platelet function significantly. Moreover, most studies looking at different priming solutions focused on patient outcome, bleeding, or changes in gross coagulation (i.e., platelet count). As the number of platelets is independent of platelet function, investigating platelet aggregability may help to evaluate the efficacy of the different priming methods.

Platelet-to-surface interaction is only the inducing process initiating the release reactions and liberation of secretory products—followed by an excessive platelet-to-platelet interaction and resulting in abnormalities in platelet function. In addition to these surface-related reasons for platelet abnormalities, various other aspects have to be taken into account including hypothermia, anesthetics, and infusion of homologous blood and drugs (5). The contribution of all these factors to platelet dysfunction after cardiac surgery remains undefined.

We conclude that the degree of alterations in platelet function secondary to blood-surface interaction might be influenced by the physical, electrochemical, biochemical, and chemical properties of the synthetic surface. The type of priming solutions may modify platelet function as well. Priming solutions consisting of dextrose, RS, and albumin can help to optimize quality of coagulation after extracorporeal oxygenation procedures. Addition of gelatin may also be of value for this purpose.

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Epidural Patient-Controlled Analgesia After Cesarean Section: Buprenorphine-0.015% Bupivacaine With Epinephrine Versus Fentanyl-0.015% Bupivacaine With and Without Epinephrine

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We compared the analgesia, side effects, and plasma concentrations of buprenorphine and fentanyl in a double-blind study of 78 parturients receiving one of these drugs by patient-controlled epidural infusion after elective cesarean section with epidural anesthesia. Patients were randomized to three epidural infusion groups: group 1 ($n = 26$), 3 μg/mL buprenorphine with 0.015% bupivacaine and 1 μg/mL epinephrine; group 2 ($n = 26$), 3 μg/mL fentanyl with 0.015% bupivacaine and 1 μg/mL epinephrine; and group 3 ($n = 26$), 3 μg/mL fentanyl with 0.015% bupivacaine. Plasma for determination of opioid concentrations was obtained in some subjects in each group at intervals up to 48 h during the infusion and in some subjects from each group at intervals after the infusion was stopped. Pain relief was similar and satisfactory in all three groups. The median overall satisfaction scores were high for all three groups. Pruritus was more common in the fentanyl groups ($P < 0.05$). However, vomiting was more disturbing to the patients and seen only with buprenorphine. No patient had a respiratory rate < 12 breaths/min. Epinephrine use was associated with a slower infusion rate ($P < 0.05$, group 2 vs 3). All patients were able to ambulate without difficulty. Mean opioid plasma concentrations did not exceed 1.5 ng/mL. Thus, epidural patient-controlled analgesia in all three groups provided excellent analgesia, permitted ambulation, and was without serious side effects. Epidural buprenorphine offered no advantages over epidural fentanyl.

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The use of epidural opioids to relieve pain after a cesarean section is effective and safe (1–5). Yet, there are untoward effects associated with the use of epidural opioids that include pruritus, nausea, vomiting, urinary retention, and respiratory depression. The onset and severity of these side effects may vary with the opioid chosen and whether it is given by continuous infusion or by bolus injection. Several approaches have been recommended to decrease the incidence of side effects. These include the use of opioids with greater lipid solubility and the addition of local anesthetics with or without epinephrine (5–7). The use of a low-dose naloxone intravenous infusion (8) or epidural droperidol (9) has also been described.

The highly lipid-soluble opioid fentanyl is widely used for epidural administration because of its low incidence of significant respiratory depression, urinary retention, and severe pruritus (1–3,10). Buprenorphine, an opioid agonist/antagonist with very high lipid solubility and affinity for the opioid receptor, provides satisfactory postoperative analgesia with few serious side effects when administered epidurally (11–15) and might be superior to fentanyl for this purpose. Studies on compatibility with spinal cord tissue and cerebrospinal fluid indicate that buprenorphine may be administered safely in the epidural space (16).

To develop a regimen with minimal opioid-induced side effects in the setting of a prolonged (>24 h) epidural infusion after cesarean section, we evaluated quality of analgesia and incidence of side

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effects of buprenorphine and fentanyl at doses found in our practice to be equipotent when given with a low (0.015%) concentration of bupivacaine and also whether epinephrine administration decreases fentanyl requirements. In addition, we assayed plasma concentrations of these opioids during and following the infusion to determine whether either drug accumulates in plasma.

Methods

The study was approved by the Institutional Review Board of the Albert Einstein College of Medicine, and written informed consent was obtained from each patient. Seventy-eight ASA physical status I–II parturients at term, scheduled for elective cesarean section under epidural anesthesia were included. Patients known to use sedatives or analgesics were excluded. After the subjects received 30 mL of 0.3 M sodium citrate and an intravenous infusion of 1.5–2 L of lactated Ringer's solution, continuous lumbar epidural anesthesia to achieve a T4-6 sensory level was established by injecting 3 mL of 3% 2-chloroprocaine with 5 μg/mL of epinephrine followed by 0.5% bupivacaine with 2 μg/mL of epinephrine via a catheter placed at the L3-4 interspace. The epidural catheter was directed cephalad 3 cm into the epidural space. No opiates were administered before or during the surgical procedure.

Upon arrival in the postanesthesia care unit, patients were randomly allocated to one of three groups: group 1 (n = 26) received continuous epidural patient-controlled analgesia (PCA) infusion of 3 μg/mL of buprenorphine with 0.015% bupivacaine and 1 μg/mL of epinephrine diluted in saline. Group 2 (n = 26) received continuous epidural-PCA infusion of 3 μg/mL of fentanyl with 0.015% bupivacaine and 1 μg/mL of epinephrine diluted in saline. Group 3 (n = 26) received continuous epidural-PCA infusion of 3 μg/mL of fentanyl with 0.015% bupivacaine diluted in saline. The solutions used had been placed in coded bags and neither the investigator nor the patient was aware of which solution was being given. The epidural catheter was connected to a portable Pancretec 5500-mini infuser (Pancretec Inc., San Diego, Calif.) and each patient received an initial infusion at the rate of 10 mL/h, with self-administered 10-mL boluses every 2 h as desired. No patient received systemic opioids or sedatives during this study. Every 4 h, or sooner if requested, an investigator evaluated the patient for each side effect and quality of analgesia, increased or decreased the infusion as needed, and administered additional 10-mL boluses if needed to achieve satisfaction. The decision that the infusion was no longer necessary was made by the patient. Pain intensity was assessed by using a 10-point visual analogue scale in which progressive changes in facial expression indicate degree of pain (0 = no pain, 10 = most severe pain). Overall satisfaction with the infusion was assessed by using a 10-point scale (0 = no satisfaction, 10 = best satisfaction). The patients were assessed for side effects using a three-point scale (1 = mild, 2 = moderate, 3 = severe). Each patient had intravenous access throughout, and vital signs were monitored every 1–2 h by a nurse. Patients started to ambulate 12–24 h after initiation of the study. The patients were assisted by a nurse during ambulation, and on each occasion heart rate and arterial blood pressure were measured at the start of ambulation.

Plasma samples for determination of levels of fentanyl and buprenorphine were obtained before and at 4, 24, 36, and 48 h after the start of infusion in some patients randomly selected from each group. In other patients randomly selected from each group, plasma for determination of opioid concentrations was obtained at the time the infusion was discontinued and at 4, 8, and 12 h later. Venous blood samples were obtained from an antecubital vein of the arm contralateral to the one with an intravenous infusion, and after separation by centrifugation, plasmas were stored at −20°C until analysis. Plasma concentrations of fentanyl were determined using a radioimmunoassay kit (Research Diagnostics, Flanders, N.J.) (17). Plasma concentrations of buprenorphine were determined by Hazelton Laboratories Corp. (Vienna, Va.) using a radioimmunoassay (18). The fentanyl assay has a limit of detection of 0.1 ng/mL and a coefficient of variation of 6.0%, and the buprenorphine assay has a limit of detection of 0.1 ng/mL and a coefficient of variation of 7.6%. Data were analyzed using repeated measures analysis of variance, Student's t-test, χ^2 or Fisher's exact test, and Wilcoxon signed-rank sum tests where appropriate. $P < 0.05$ was considered significant.

Results

There were no differences among the groups with respect to age, height, weight, gravity, or parity. Pain relief was satisfactory and similar in all three groups throughout the study (Table 1). The median overall satisfaction score was 9 for group 1, 9.5 for group 2, and 10 for group 3. The satisfaction score was higher in group 3 ($P < 0.05$, Wilcoxon rank sums) when compared with groups 1 or 2. The durations of infusions for groups 1, 2, and 3 did not differ significantly (Wilcoxon rank sums) and were 42 ± 2.0 h, 47.8 ± 2.0 h, and 44.8 ± 2.9 h, respectively. Infusion rates during the first 44 h were higher for group 3 than for groups 1 or 2 (Figure 1) ($P < 0.05$). In

Table 1. Pain Scores

Time of study	Group 1	*n*	Group 2	*n*	Group 3	*n*
0 h	0 0	26	0 0	26	0 0	26
1 h	0 0	26	0 0	26	0 0	26
4 h	2.8 ± 0.4	26	3.0 ± 0.5	26	2.9 ± 0.6	26
8 h	1.9 ± 0.4	26	2.4 ± 0.4	26	3.8 ± 0.5	26
24 h	1.9 ± 0.4	24	2.5 ± 0.5	26	2.8 ± 0.4	24
36 h	1.8 ± 0.4	23	1.7 ± 0.4	25	2.0 ± 0.5	20
48 h	0.7 ± 0.2	8	0.9 ± 0.3	12	1.6 ± 0.4	13

Pain scale: 0 = no pain, 10 = most severe pain.
Value are mean ± SE. Data were analyzed by repeated-measures analysis of variance. There were no significant differences among the groups.

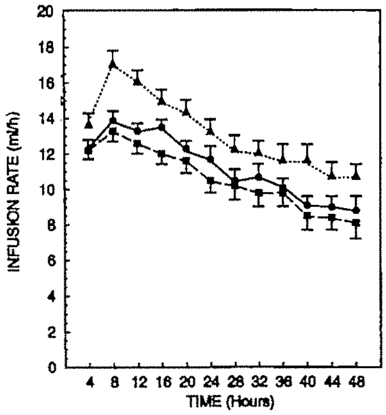

Figure 1. Epidural-PCA infusion rates. Values are mean ± SE. Data were analyzed by repeated-measures analysis of variance. Infusion rates during the first 44 h were faster for group 3 (▲) than for group 1 (●) or 2 (■) ($P < 0.05$).

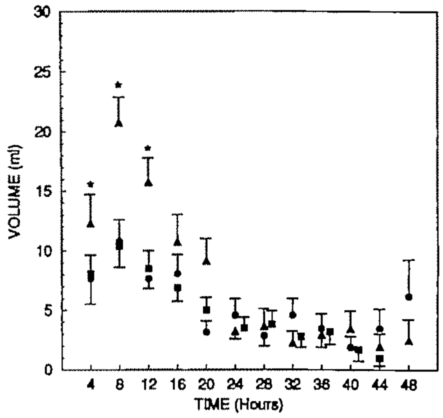

Figure 2. Supplemental study solution received after patient initiated requests. Values are mean ± SE. Data were analyzed by repeated-measures analysis of variance. Values are the total for the preceding 4-h interval. Group 1 (●), group 2 (■), group 3 (▲). *$P < 0.01$, group 3 vs group 1 or 2.

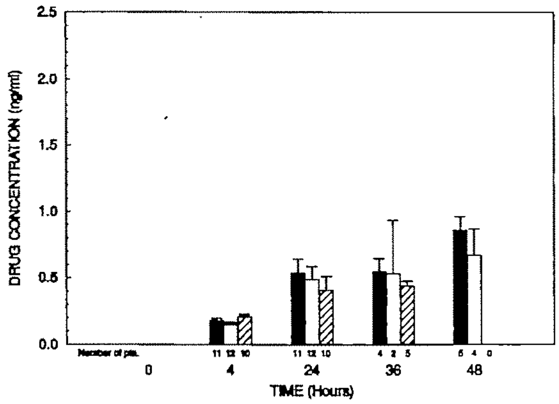

Figure 3. Plasma concentrations of fentanyl and buprenorphine are shown as mean ± SEM. No samples were obtained from group 3 patients at the 48-h time. Data for groups 2 and 3 were compared by Student's *t*-test. There were no significant differences between these groups. Group 1, *filled bar*; group 2, *open bar*; group 3, *hatched bar*.

contrast, there were no differences in the infusion rates between groups 1 and 2 during the same time period. The amount of volume received as boluses was significantly larger ($P < 0.01$) for group 3 when compared with groups 1 or 2 during the first 12 h of the study (Figure 2). The total incidence of pruritus for patients in group 1 (30.8%) was lower than that for group 2 (65.4%) or 3 (73.1%) ($P < 0.05$, Fisher's exact test). Pruritus was mild in most patients in all three groups. Severe pruritus requiring treatment occurred in one patient in group 2 and in three patients in group 3. The rostral spread of pruritus was limited and of the total number of patients who experienced pruritus, facial pruritus was present in only one of the eight in group 1, three of the 17 in group 2, and seven of the 19 in group 3. Sedation was common and occurred with similar frequency in all the groups (69.2% in group 1, 65.4% in group 2, and 73.1% in group 3). Sedation was never more than mild, and no patient complained about the degree of sedation. The total incidence of nausea for patients in group 1 (38.5%) was higher ($P < 0.05$) than for group 2 (3.8%) or 3 (3.8%). Nausea occurred in group 1 patients throughout the 48 h but did not occur in group 2 or 3 patients after 4 h. Vomiting was seen only in five buprenorphine-treated patients, and this occurred within the first 6 h of the study. No patient had a respiratory rate <12 breaths/min. One patient in group 1 required treatment for a single episode of urinary retention 6 h after removal of the urethral catheter. Patients did not complain of lower extremity sensory loss, and all were able to ambulate easily. Plasma opioid concentrations during 48 h of the study are shown in Figure 3. Groups 2 and 3 did not differ in mean plasma opioid concentrations (Figure 3). In the subset of patients in which plasma opioid concentrations were measured at the time of termination of the opioid infusion and at intervals thereafter, those in groups 1 and 2 demonstrated an increase in mean plasma opioid levels 4 h after the

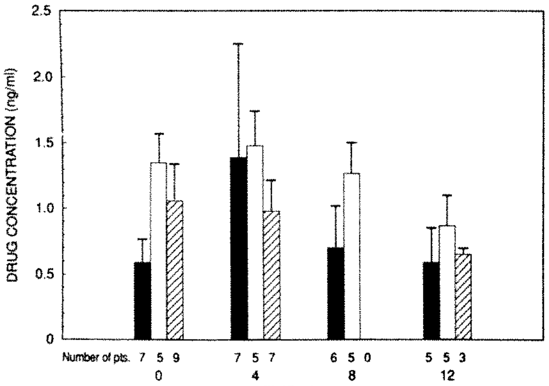

Figure 4. Plasma fentanyl and buprenorphine concentrations were obtained in a subset of patients at the time of discontinuation of the epidural-PCA infusion and at intervals thereafter. In this subset of patients, the epidural-PCA infusion was discontinued at 16–70 h. No samples were obtained from group 3 patients at the 8-h time. Data for groups 2 and 3 were compared by Student's *t*-test and there were no significant differences. The increase from baseline seen at the 4-h time point in group 1 was significant ($P < 0.05$, Wilcoxon signed-rank sum). Group 1, *filled bar;* group 2, *open bar;* group 3, *hatched bar.*

end of the infusion (Figure 4). However, this change was significant ($P < 0.02$, Wilcoxon signed-rank sum) for group 1 only. In one subject in group 1, buprenorphine plasma levels increased from 0.96 to 3.88 ng/mL at 4 h after the infusion was stopped.

Discussion

The goal of our study was to develop a regimen that provided prolonged (>24 h), effective postcesarean section pain relief, without interfering with ambulation and with minimal opioid-induced side effects. Epidural-PCA with all three regimens produced excellent analgesia without serious side effects. Mean opioid plasma concentrations during the infusion did not exceed 1.0 ng/mL in any group. Patients in all three groups could easily ambulate and were very satisfied. Buprenorphine at doses producing a comparable satisfactory analgesic effect caused a similar incidence of sedation, a lower incidence of pruritus, but a higher incidence of nausea and of vomiting, the side effect most disturbing to the patients, than did fentanyl. Sedation was never more than mild. Ellis et al. (19), in a study in which postcesarean section patients received fentanyl titrated to their requested level of analgesia by either intravenous or epidural infusion for 24 h, were unable to achieve adequate pain relief at their maximum allowable infusion rate in 25% of the patients in the intravenous group. Excessive somnolence occurred in 33% of patients in their intravenous group and in 12.5% of patients in their epidural group. Pruritus severe enough to require treatment occurred in 11.5% of our patients who received fentanyl-bupivacaine and 3.8% of our patients who received fentanyl-bupivacaine-epinephrine. This is substantially lower than the incidence of 22% for postcesarean section patients receiving fentanyl-bupivacaine or 42% of postcesarean section patients receiving morphine-bupivacaine for 24 h by epidural infusion set at a constant rate reported by Fischer et al. (2). The incidence of nausea of 3.8% in both our fentanyl groups is similar to the 3.4% for the fentanyl group and substantially lower than the 17.4% for the morphine group reported by these investigators. The incidence of nausea of 38.5% in our buprenorphine group is double that of their morphine group. Ellis et al. (19) provide no information on the incidence of pruritus or nausea in either of their groups.

We have found that the addition of bupivacaine (0.03%) to epidural fentanyl produces marked leg numbness and consequent difficulty with ambulation in a substantial percentage of patients (20). In the present study, in the hope of reducing the opioid requirement without causing lower extremity sensory loss, we added bupivacaine (0.015%) to the epidural infusion. We provided satisfactory analgesia with a substantially lower amount of fentanyl than was needed in the study by Ellis et al. (19) in which patients receiving fentanyl alone by epidural infusion for pain relief after cesarean section were titrated to their requested level of analgesia. Whether in fact the low concentration of bupivacaine that we used permitted us to administer smaller amounts of opioid than would otherwise have been required needs to be confirmed.

Consistent with prior studies (5,6,21,22), we found that the addition of epinephrine to epidural fentanyl and bupivacaine reduced the total drug requirement without affecting the incidence of side effects. However, in contrast to a prior report (7), in our study the addition of epinephrine did not reduce plasma fentanyl concentrations.

After termination of the opioid infusion, we observed a marked increase in plasma buprenorphine level and a small increase, which did not achieve statistical significance, in plasma fentanyl concentration when epinephrine was present in the solution. The possibility that for several hours after cessation of epinephrine-containing epidural opioid infusions systemic opioid absorption may occur at a rate sufficient to increase plasma opioid levels should be considered when switching patients from these infusions to oral opioid analgesics.

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Plasma Inorganic Fluoride With Sevoflurane Anesthesia: Correlation With Indices of Hepatic and Renal Function

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The biotransformation and plasma inorganic fluoride ion production of sevoflurane (the new volatile anesthetic) during and after surgical anesthesia was studied in 50 ASA I or II surgical patients. Twenty-five additional patients served as controls by receiving isoflurane. Sevoflurane or isoflurane was administered with a semiclosed (total gas flow, 2 L/min O_2) circle absorption system for durations of 1.0 to greater than 7.0 minimal alveolar concentration (MAC) hours for surgical anesthesia (sevoflurane MAC, 2.05%; isoflurane MAC, 1.15%). Preoperative and postoperative blood urea nitrogen and creatinine concentrations were determined. Blood samples were obtained during and after anesthesia in both groups for determining anesthetic blood concentration analysis and plasma fluoride level. Plasma fluoride concentrations did not significantly increase during isoflurane anesthesia. Sevoflurane biotransformation produced a mean peak plasma inorganic fluoride concentration of 29.3 ± 1.8 μmol/L, 2 h after anesthesia, which decreased to 18 μmol/L concentration by 8 h after anesthesia. The peak plasma inorganic fluoride ion concentration correlated with duration of sevoflurane anesthetic exposure. Five patients given sevoflurane had peak levels transiently exceeding 50 μmol/L; and one of these had a history of ingesting drugs potentially producing hepatic enzyme induction. No increases in postoperative levels of creatinine, blood urea nitrogen, direct bilirubin, or hepatic transaminase and no changes in serum electrolyte level occurred in either anesthetic group. Indirect bilirubin concentration increased significantly after sevoflurane anesthesia, but the increase was not of clinical significance (from 0.30 ± 0.03 to 0.38 ± 0.06 mg/dL). Indirect bilirubin concentrations did not increase after isoflurane anesthesia; the concentrations reached 0.31 ± 0.04 mg/dL and did not differ significantly from those found with sevoflurane. Even though plasma fluoride concentrations increased, no evidence of renal dysfunction occurred.

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Sevoflurane [CH_2 F-O-CH $(CF_3)_2$], (fluoromethyl 2,2,2 trifluoro-1-[trifluoro methyl] ethyl ether), is a fluorinated derivative of ethyl isopropyl ether. Sevoflurane has a blood-gas partition coefficient of 0.60 (1) that allows a rapid induction of anesthesia and emergence (1,2). The low blood solubility and rapid elimination of sevoflurane also should limit the metabolism of this agent.

Previous in vitro investigations have shown that sevoflurane undergoes considerable metabolism (3). In vivo studies in animals have shown sevoflurane produces peak serum fluoride values similar to those of enflurane anesthesia with no renal defect resulting (3,4). A previous study in human volunteers exposed to 2%–3% sevoflurane (minimum alveolar concentration [MAC], 2.05% in humans) (5) showed peak serum inorganic fluoride concentrations averaging 22 μmol/L (2). Fluoride production after surgical anesthesia has been evaluated in the Japanese population (6); however, studies after surgical anesthesia of various durations in North American populations have not been reported. In this study, we report the serum inorganic fluoride levels produced during and after sevoflurane anesthesia compared with isoflurane anesthesia in healthy surgical patients.

Methods

Seventy-five surgical patients (ASA I or II) were randomized to receive either sevoflurane or isoflurane anesthesia: 50 patients received sevoflurane and 25, isoflurane. The protocol was approved by the

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Table 1. Hematologic and Hepatorenal Function Tests

	Sevoflurane		Isoflurane	
	Preoperative	Postoperative	Preoperative	Postoperative
Hemoglobin (g/dL)	12.4 ± 1.6	11.3 ± 0.2[a]	12.0 ± 1.7	10.8 ± 0.3[a]
WBC count (μL^{-1})	8.0 ± 0.9	9.4 ± 0.4	7.0 ± 0.5	9.3 ± 0.4[a]
Platelet count (μL^{-1})	275 ± 11.9	270 ± 11.3	288 ± 18.1	276 ± 15.8
Sodium (mmol/L)	139 ± 2	138 ± 3	139 ± 2	139 ± 3
Potassium (mmol/L)	4.1 ± 0.4	4.0 ± 0.3	4.1 ± 0.3	4.0 ± 0.3
Uric acid (mg/dL)	4.3 ± 1.2	3.8 ± 1.2	3.9 ± 1.0	3.3 ± 1.0[a]
AST (SGOT) (IU/L)	22 ± 1	23 ± 1	21 ± 1	21 ± 1
ALT (SGPT) (IU/L)	17 ± 1	15 ± 1[a]	14 ± 1	12 ± 1[a]
Alkaline phosphatase (IU/L)	59 ± 3	52 ± 3[a]	58 ± 4	50 ± 4[a]
Bilirubin				
Direct (mg/dL)	0.21 ± 0.01	0.23 ± 0.02	0.20 ± 0.02	0.20 ± 0.02
Indirect (mg/dL)	0.30 ± 0.03	0.38 ± 0.06[a]	0.27 ± 0.04	0.31 ± 0.04
Creatinine (mg/dL)	0.86 ± 0.03	0.81 ± 0.02[a]	0.89 ± 0.08	0.78 ± 0.03[a]
BUN (mg/dL)	11.9 ± 0.6	7.3 ± 0.4[a]	12.4 ± 0.7	6.4 ± 0.8[a]
Urine pH	6.38 ± 1.1	6.7 ± 0.1	5.9 ± 1.0	6.7 ± 0.2
Urine specific gravity	1.02 ± 0.01	1.01 ± 0.00	1.02 ± 0.01	1.01 ± 0.01

AST (SGOT), aspartate aminotransferase (serum glutamine oxaloacetic transaminase); ALT (SGPT), alanine aminotransferase (serum glutamic pyruvic transaminase); BUN, blood urea nitrogen.

No differences exist between values for sevoflurane ($n = 49$) and isoflurane ($n = 25$) groups preoperatively and postoperatively.

[a] Differs from preoperative value, $P < 0.05$.

Institutional Review Board Human Subjects Committee of the University of Arizona Health Sciences Center, and written informed consent was obtained from all patients. Preoperative measurements of serum uric acid, creatinine, and urea nitrogen levels and routine urinalysis were performed.

Before anesthetic inductions, venous blood samples were obtained for determination of plasma fluoride concentrations. Thirty minutes after receiving midazolam (0.01–0.03 mg/kg IV), the patient (while breathing oxygen) was anesthetized with an intravenous injection of 3–5 mg/kg of thiopental and either 1–2 mg/kg of succinylcholine or 0.1 mg/kg of vecuronium for paralysis. Ventilation was controlled via a mask with the inspired concentration of (2–2.5 MAC) sevoflurane or isoflurane before tracheal intubation. Anesthesia after endotracheal intubation was maintained using either sevoflurane or isoflurane administered in 100% oxygen. Blood samples were obtained from a heparin-flushed catheter at hourly intervals during anesthetic delivery, and once at the end of anesthetic delivery for plasma fluoride concentration determination. Surgical anesthetic concentrations were delivered until surgical wound closure was completed. Controlled ventilation was maintained for 1 min after anesthetic discontinuation, and spontaneous ventilation was allowed to return.

Venous blood samples for plasma fluoride analysis were obtained 1, 2, 3, 8, and 24 h after anesthesia. The MAC hours for sevoflurane and isoflurane exposures were calculated from percent anesthetic concentration and duration of anesthetic exposure. The MAC values used were 2.05% for sevoflurane and 1.15% for isoflurane.

Plasma inorganic fluoride analysis was performed using an ion-selective electrode (Orion Research, Cambridge, Mass.) calibrated against standard solutions of sodium fluoride (1–100 μmol/L).

Preoperative and postoperative electrolyte and renal function tests were compared between anesthetics using two-way analysis of variance. Regression analysis was used to evaluate the correlation of plasma fluoride concentration and anesthetic duration. A P value of <0.05 was considered significant.

Results

Data from 25 isoflurane-anesthetized patients and 49 sevoflurane-anesthetized patients were included for analysis. One patient in the sevoflurane group was excluded owing to preoperatively unrecognized neurologic disease. (The peak plasma fluoride value for this patient was 13.7 μmol/L.)

Patients anesthetized with either sevoflurane or isoflurane did not differ preoperatively in age, height, weight, or body mass index (see Table 1 of preceding article). Preoperative and postoperative changes in levels of serum electrolytes, uric acid, blood urea nitrogen, serum creatinine, hepatic transaminases, and direct bilirubin did not differ between sevoflurane and isoflurane groups (Table 1). Indirect bilirubin levels increased after sevoflurane anesthesia ($P < 0.05$) but was not of clinical significance. Isoflurane anesthesia did not result in an increase in indirect

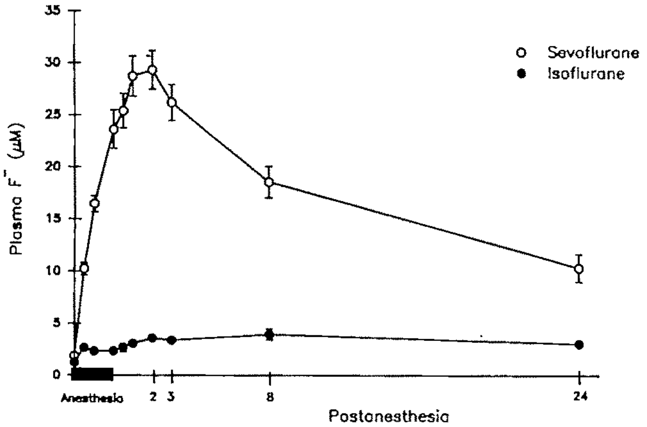

Figure 1. Mean plasma inorganic fluoride concentration during and after isoflurane or sevoflurane anesthesia. The mean peak value for isoflurane is 3.94 ± 0.5 μmol/L and for sevoflurane, 29.3 ± 1.8 μmol/L. Data points shown are mean ± SEM. Anesthesia time = mean anesthesia time for all cases.

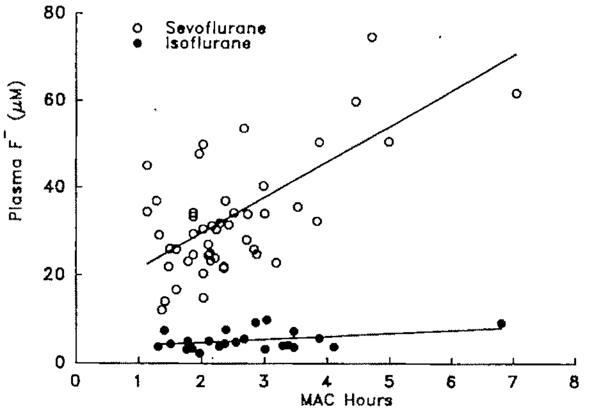

Figure 2. Correlation between individual peak plasma inorganic fluoride values for sevoflurane- and isoflurane-anesthetized patients and MAC-hours. A positive correlation was demonstrated only for sevoflurane anesthetic duration and peak plasma fluoride concentration, $r = 0.65$, $P < 0.01$.

bilirubin concentrations postoperatively. Postoperative values for indirect bilirubin concentration did not differ between the sevoflurane and isoflurane groups.

Among patients anesthetized with isoflurane, plasma inorganic fluoride concentration increased with peak levels (3.9 ± 0.5 μmol/L) occurring 8 h after anesthetic discontinuation. The maximum value recorded for any patient in the isoflurane-anesthetized group was 9.3 μmol/L (Figure 1).

A larger quantity of inorganic fluoride was produced after sevoflurane anesthesia (Figure 1). Peak plasma fluoride concentrations (29.3 μmol/L) occurred 2 h after anesthetic discontinuation. By 8 h, the plasma fluoride level had decreased to 18 μmol/L; and by 24 h, the concentration was less than 10 μmol/L.

A positive correlation was found for the relationship between anesthetic dose and peak plasma inorganic fluoride concentration in patients anesthetized with sevoflurane (r, 0.65, $P < 0.01$). No positive relationship was demonstrated for the isoflurane with respect to MAC hours and peak plasma inorganic fluoride values (Figure 2).

Discussion

Sevoflurane undergoes biotransformation with the production of free fluoride ions (3,4) that appear to be largely derived from the fluoromethyl group of sevoflurane after metabolic cleavage of the ether (Figure 3). The stoichiometry of fluoride production is one fluoride ion produced for each sevoflurane ion biotransformed. Our results showed that sevoflurane is readily biotransformed, producing a mean peak serum fluoride concentration of 29.3 ± 1.8 μmol/L for all patients after surgical anesthesia with sevoflurane and oxygen.

The administration of methoxyflurane in animals and humans can produce a dose-related effect on the renal-concentrating ability, which is related to the production of excess fluoride through biotransformation (7,8). Studies evaluating methoxyflurane-induced nephrotoxicity have recorded a renal-concentrating defect only when serum organic fluoride levels exceeded 50 μmol/L (9). The peak plasma fluoride concentrations in our patients after sevoflurane anesthesia were well below this level.

Enflurane anesthesia is also capable of producing increased serum fluoride concentrations with a profile somewhat more similar to that of sevoflurane (where serum fluoride concentrations decrease within 24–48 h after anesthesia rather than remain elevated for several days as occurs after methoxyflurane anesthesia). The threshold for enflurane-related fluoride-induced alteration in maximum renal-concentrating ability when tested using vassopressin injection was detectable when peak serum fluoride

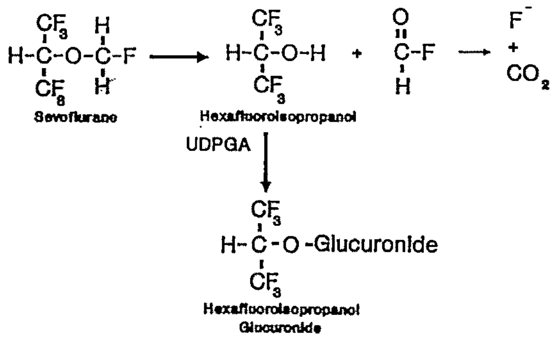

Figure 3. Proposed biotransformation of sevoflurane. UDPGA, uridine diphosphate glucuronic acid.

levels exceeded 33 μmol/L (10). In our study, the mean peak plasma fluoride value for all patients receiving sevoflurane anesthesia still did not exceed this level. No patient in our study had significant changes in levels of electrolytes, blood urea nitrogen, or creatinine compared with that of the isoflurane group during the preoperative and postoperative periods.

Examination of the fluoride-induced nephrotoxic potential of inhaled anesthetics must take into account the degree of metabolism of the agent and its duration of availability for metabolism. A discrepancy between the in vitro rates of defluorination of sevoflurane and its in vivo serum fluoride levels after anesthesia in rats has been observed. That is, sevoflurane in hepatic microsomes was defluorinated at a rate similar to methoxyflurane, yet, in whole animal studies, the peak fluoride levels were one-fourth those of methoxyflurane (11). This is undoubtedly due to the rapid elimination of sevoflurane (see Figure 4, preceding article) through the pulmonary route compared with the greater solubility of methoxyflurane that allows more extensive metabolism of the drug to occur. This phenomenon may also exist to a lesser extent when sevoflurane is compared with enflurane. The mean peak plasma fluoride level for all patients studied was 29.3 μmol/L, occurring 2 h after anesthesia. This peak inorganic fluoride level is similar to that produced in volunteers 6 h after enflurane exposure in a study by Mazze et al. (10). However, the area under the curve for fluoride production and elimination of the two anesthetics differs in that fluoride levels in the blood by 8 h after anesthesia with enflurane (blood-gas partition coefficient, 1.9) were still approximately 32 μmol/L, whereas comparable 8-h fluoride levels after sevoflurane anesthesia in our study were 18.9 μmol/L. It is probably not only the peak serum fluoride level that is responsible for producing nephrotoxicity but also the length of time that the kidney is exposed to high concentrations of fluoride (10,12). The rapid decrease in plasma inorganic fluoride levels after sevoflurane anesthesia may prevent development of a plasma fluoride profile capable of producing a renal-concentrating defect. Studies in Fisher 344 rats anesthetized with sevoflurane (1.4% concentration) for 4 h have shown levels of fluoride production (29.1 μmol/L peak) consistent with our results (in humans), which do not result in a renal defect (3).

Prolonged sevoflurane exposure (average 4.7 MAC hours) in five of our patients produced higher peak plasma fluoride values of 50 μmol/L. Though no abnormalities in serum electrolytes, blood urea nitrogen, or creatinine occurred in any of these patients, discrete abnormalities in renal-concentrating ability were not evaluated in this study. It is uncertain if this fluoride level after sevoflurane anesthesia is capable of producing a concentrating abnormality in humans.

The ability for hepatic enzyme induction to increase sevoflurane metabolism has been evaluated to a limited extent in previous studies. Phenobarbital can increase sevoflurane metabolism in Fisher 344 rats but to a lesser extent than the increase in defluorination produced by phenobarbital pretreatment before methoxyflurane anesthesia (4). Isoniazid has been shown to increase sevoflurane defluorination in rat hepatic microsomes (11). The observed increase in metabolism was less than that which occurred with enflurane but greater than that with isoflurane. Ethanol ingestion in rats has also been shown to increase sevoflurane metabolism and to result in an increase in inorganic fluoride production (13). It is unclear whether enzyme induction played a role in the fluoride production level in some of our patients. One patient anesthetized with sevoflurane had an unusually high fluoride level (62 μmol/L) after 3.5 MAC hours of anesthesia. This patient had an undisclosed preoperative history of prescription drug abuse that included valium and codeine use. In addition, the patient admitted he used pentobarbital for 4 days preoperatively in combination with valium in an unspecified quantity for anxiety symptoms. The possible role of these drugs on the extent of sevoflurane metabolism in this patient is unclear; however, the higher fluoride concentrations for this duration of sevoflurane exposure suggest a possible role for an enzyme-induction–related increase in anesthetic metabolism in this patient.

Our results of fluoride production after isoflurane anesthesia are comparable to those of previously reported results with peak serum fluoride values of less than 10 μmol/L in all patients (14).

Sevoflurane was delivered using a semiclosed anesthetic circuit with soda lime for CO_2 absorption. Questions regarding sevoflurane degradation with CO_2 absorption materials have emerged (15); however, recent studies have shown that sevoflurane can be delivered safely with soda lime in a semiclosed anesthetic circuit (16). As our laboratory investigations with sevoflurane show, no evidence of organotoxicity was evident. There was no postoperative elevation of hepatocellular enzymes, although indirect bilirubin concentrations after sevoflurane anesthesia increased compared with preoperative values. The postoperative values did not differ from that of the sevoflurane group, and the increase was of no clinical significance.

Our study demonstrates that sevoflurane delivery to surgical patients produced a mean peak serum fluoride level of 29 μmol/L with a rapid decrease in serum fluoride levels to almost half this value by 8 h after anesthetic discontinuation. No evidence of abnormal renal function occurred in any of the patients exposed to sevoflurane in the postoperative period; however, an effect on the renal-concentrating ability after sevoflurane was not evaluated. In healthy patients, postoperative renal dysfunction appears to be unlikely with sevoflurane anesthesia as its low blood-gas solubility coefficient and rapid elimination may preclude prolonged elevated levels of fluoride and resultant renal dysfunction.

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Plasma Fluoride Concentrations During and After Prolonged Anesthesia: A Comparison of Halothane and Isoflurane

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Serum inorganic fluoride concentrations were studied in 19 adult patients undergoing prolonged head and neck surgery with either halothane or isoflurane anesthesia (mean 19.5 and 19.2 MAC-hours, respectively). In the group of nine patients anesthetized with isoflurane, plasma inorganic fluoride increased from a mean concentration of 3.5 μmol/L (baseline) to a peak of 43.2 μmol/L. Forty percent of the patients in the isoflurane group had peak plasma inorganic fluoride concentrations of more than 50 μmol/L. In the group that received halothane, plasma inorganic fluoride concentrations increased from a mean of 3.8 μmol/L to a peak of 12.6 μmol/L. Despite similar exposures to both anesthetics, the differences in serum inorganic fluoride concentrations between the two groups were significant at 10, 24, and 48 h after induction of anesthesia ($P = 0.035$, $P = 0.003$, and $P = 0.003$, respectively). Serum electrolyte, urea, and creatinine concentrations and urine output rates during and after surgery were similar in both groups. We conclude that, after anesthesia of up to 20 MAC-hours, metabolism of isoflurane to inorganic fluoride may be of a greater magnitude than has previously been realized. Although no clinical or biochemical evidence was found to suggest postoperative renal dysfunction, we recommend caution using isoflurane when prolonged anesthesia and surgery are planned.

(Anesth Analg 1992;74:236–40)

None of the inhaled anesthetics now in use has any known direct nephrotoxic effect. However, because volatile anesthetics are fluorinated to reduce their flammability, they may, in theory, be potentially nephrotoxic. The kidney is especially susceptible to damage from drugs or toxins because of its larger perfusion and the increased concentration of excreted compounds that occur in renal tubular cells during absorption and secretion. Renal toxicity owing to biodegration of anesthetics to reactive intermediates or toxic products such as fluoride ions increases as peak serum fluoride concentrations increase above 50 μmol/L (1). Subclinical toxicity has been reported at lower concentrations for extended periods (2).

In selecting anesthetics for prolonged administration, possible nephrotoxic potential resulting from extended exposure should be considered. Even though isoflurane is associated with the least degree of biotransformation of all the fluorinated hydrocarbon anesthetics (only 0.2%–0.3% of a given dose is metabolized), we sought to determine whether prolonged anesthesia with either halothane or isoflurane produced clinically significant increases in serum inorganic fluoride.

Methods

Nineteen adult patients, aged 20–75 yr, undergoing prolonged head and neck reconstructive surgery were included in the study. They were randomly assigned to receive halothane ($n = 10$) or isoflurane ($n = 9$). Ethical approval and informed consent were obtained. Patients with evidence of renal disease, either clinical or biochemical, or who had received an inhaled anesthetic in the preceding 3 mo were excluded from the trial. Patients with a history of alcohol abuse were also excluded from the study. No patient was taking drugs known to induce liver enzymes or affect renal function.

No premedication was given. All patients received a similar anesthetic sequence. This included fentanyl (5 μg/kg IV) and an intravenous dose of thiopental sufficient to obtund the eyelash reflex, with neuromuscular blockade achieved by intravenous atracurium (0.5 mg/kg). After nasotracheal intubation, an-

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esthesia was maintained by adjusting the inspired concentration of the anesthetic to achieve an alveolar concentration of approximately 2 MAC, equal to 2.4% for isoflurane and 1.4% for halothane, in air and oxygen (FIO$_2$ = 0.4). Ventilation was adjusted to maintain normocapnea. Oxygen saturation was monitored throughout the procedure and remained within normal limits. Analysis of arterial blood gases was determined intermittently.

End-tidal concentrations of halothane and isoflurane were measured with an Engstrom Emma agent monitor, and MAC-hours of each anesthetic were calculated and corrected for patient age (3). (MAC-hour = anesthesia time [hours] × MAC value administered, in this study an average of 2 MAC of each anesthetic per hour.) Electrocardiogram, skin and core temperature, direct arterial blood pressure, and central venous pressure were continuously monitored. During surgery and after operation, the volume of fluid administered, including blood, was carefully titrated against hemodynamic status, urinary output, and a desired hematocrit of between 30% and 33%. Considerable attention was given to maintaining the hematocrit within this range to ensure optimal perfusion in the microvascular anastomoses of the free flaps used to reconstruct the surgical defects.

A modest, controlled reduction of arterial blood pressure was used throughout the procedure to facilitate surgical access and to reduce blood loss. The arterial blood pressure was maintained at an average value of 100 mm Hg (systolic) in each case. This was achieved by maintaining an alveolar concentration of anesthetic of approximately 2 MAC. If necessary, increases in arterial pressure were treated by bolus doses of intravenous fentanyl. No systolic blood pressure lower than 80 mm Hg was recorded, and vasopressors were not used.

Arterial blood samples for measurement of plasma fluoride were collected before operation, at 5 h after induction of anesthesia, and at 10 h after induction of anesthesia (when surgery was usually completed). These measurements were repeated at 24 and 48 h after induction of anesthesia.

After separation of the plasma, ionic fluoride concentrations were determined by direct ion-selective potentiometry using a specific ion fluoride electrode in conjunction with a combination pH electrode (Microprocessor ionalyzer/901 Orion Research Ltd.). This forms a differential cell very sensitive to low concentrations of fluoride. When compared with the performance of a single fluoride electrode plus an Ag/AgCl reference electrode, the differential cell is not only as consistent and accurate but also has a much shorter response time (2 vs 20 min) and requires a much smaller sample volume (0.05 vs 1.0 mL). All reference solutions were made up using double-deionized water, and care was taken to avoid contamination from glassware. Interassay coefficients of variation were 2.5% and 1.8% at mean plasma fluoride concentrations of 2.4 and 40 μmol/L, respectively. The lower limit for estimation of fluoride was 0.5 μmol/L, with linearity from this limit of detection to 95 μmol/L (linear correlation coefficient, *r* = 0.98).

Table 1. Patient Details

	Halothane (*n* = 10)	Isoflurane (*n* = 9)
Age (yr)	64.8 (6.56)	53.4 (13.5)
Weight (kg)	72.8 (5.39)	69.0 (10.9)
Male	7	5
Female	3	4

Values are mean ± SD.

Table 2. Isoflurane Patients: Operative Data

Patient No.	MAC	Anesthesia time (h)	Dose (MAC-hours)
1	2.0	9.8	19.6
2	2.1	9.6	20.2
3	1.8	10.2	18.4
4	1.9	10.7	20.3
5	2.0	9.5	19.0
6	2.0	9.1	18.2
7	1.8	10.3	18.5
8	1.9	10.1	19.2
9	1.8	10.5	19.0
Mean	1.9	9.9	19.2
(±SD)	(0.11)	(0.52)	(0.76)

Further arterial blood samples were taken before operation, at the 24-h interval, and at the 48-h interval for estimating serum urea, electrolytes, and creatinine. Diuretics were not administered either during or after operation. Hourly urine output was recorded. Statistical analysis of the data from the two study groups was performed using the χ^2-test, and paired and unpaired *t*-tests where appropriate. A value of *P* less than 0.05 was considered significant.

Results

The preoperative and operative details of the 19 patients who were studied are outlined in Tables 1, 2, and 3. No significant variation between the two groups was observed before operation. Mean (SD) exposure to halothane and isoflurane in both groups was similar: 19.5 (1.72) and 19.2 (0.76) MAC-hours, respectively. A continuous linear increase in serum fluoride concentration occurred during operation in those patients who received isoflurane. This increase continued after operation until peak fluoride concen-

Table 3. Halothane Patients: Operative Data

Patient No.	MAC	Anesthesia time (h)	Dose (MAC-hours)
1	2.1	10.2	21.6
2	1.8	11.3	20.16
3	1.7	10.5	17.8
4	2.0	10.0.	20.0
5	1.8	9.2	16.6
6	1.9	9.8	18.6
7	2.0	10.6	21.2
8	1.9	9.5	18.1
9	2.1	10.2	21.5
10	1.9	9.9	18.8
Mean	1.9	10.2	19.5
(±SD)	(0.13)	(0.59)	(1.72)

trations were reached (24 h after induction of anesthesia). In the group of patients who received halothane, an increase was also observed; however this increase was not continued into the period after operation, and peak serum inorganic fluoride concentrations occurred at 10 h (approximate end of anesthesia and surgery). Despite similar exposures to both anesthetics, there were differences in mean serum fluoride concentrations between the two groups at the 10-, 24-, and 48-h time interval. These differences were statistically significant ($P = 0.035$, $P = 0.003$, and $P = 0.003$, respectively).

From a mean baseline value of 3.5 μmol/L (which is within the average range quoted in recent work [4–6]), 40% of patients who received a lengthy anesthetic with isoflurane had peak serum fluoride levels of more than 50 μmol/L at 24 h after induction of anesthesia. The fluoride concentrations of the remaining patients in the isoflurane group also peaked at 24 h, but none of these concentrations was above 50 μmol/L (Figure 1).

After operation, concentrations of serum urea, creatinine, and electrolytes in both groups of patients demonstrated no significant difference from baseline measurements (Table 4). Mean (SD) hourly urine output in the two groups was within normal limits throughout the study period: 66.4 (6.3) mL/h for halothane and 73.2 (7.8) mL/h for isoflurane.

Twenty patients were initially included in the study. However, one patient with the highest peak fluoride concentration (82.3 μmol/L) deviated from the experimental design by having a second exposure to isoflurane within 2 h of completion of the first surgical procedure and was excluded from the trial. This observation was made 24 h after induction of the first anesthetic. The total exposure time was 23.6 MAC-hours. This patient's biochemistry and urinary output remained within the normal range throughout the study period.

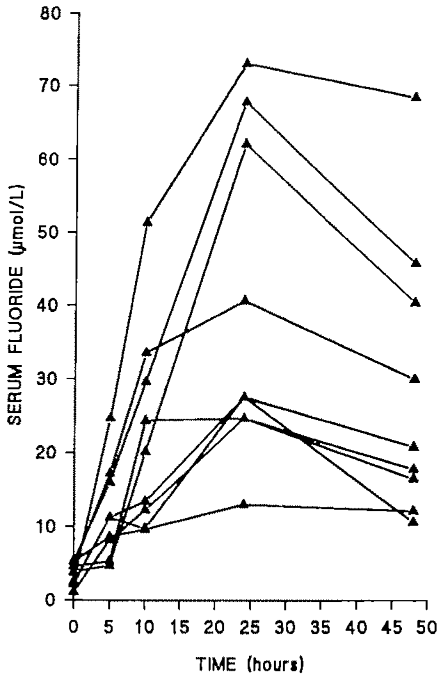

Figure 1. Serum fluoride changes after prolonged anesthesia with isoflurane.

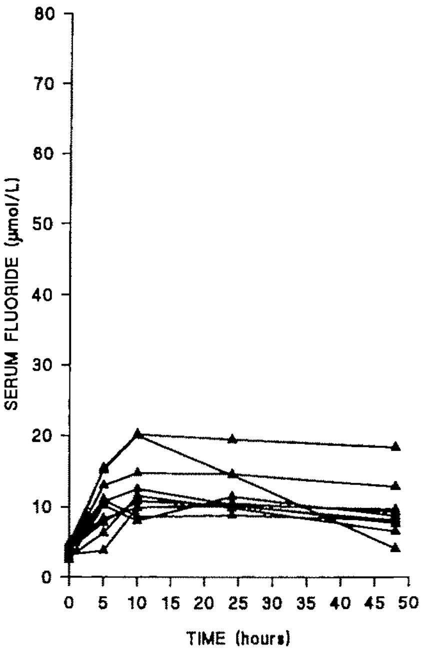

Figure 2. Serum fluoride changes after prolonged anesthesia with halothane.

Discussion

In 1966 Crandell and colleagues (7) reported renal failure in 13 of 41 patients receiving methoxyflurane anesthesia for abdominal surgery. The clinical picture consisted of a dose-related, polyuric, renal insuffi-

Table 4. Mean Serum Urea, Creatinine, and Electrolyte Concentrations

	Baseline	24 h	48 h
Isoflurane (n = 9)			
Sodium (mmol/L)	142 (0.3)	143 (0.4)	140 (0.20)
Potassium (mmol/L)	4.5 (0.2)	4.6 (0.3)	4.0 (0.1)
Chloride (mmol/L)	104 (1.1)	105 (1.4)	106 (1.3)
Bicarbonate (mmol/L)	26.2 (0.6)	26.7 (0.4)	27.1 (0.3)
Creatinine (μmol/L)	119 (10.1)	125 (11.7)	124 (11.1)
Urea (mmol/L)	6.4 (0.4)	7.8 (0.7)	5.4 (0.3)
Halothane (n = 10)			
Sodium (mmol/L)	141 (1.2)	138 (0.7)	142 (0.5)
Potassium (mmol/L)	4.3 (0.1)	4.6 (0.3)	4.0 (0.2)
Chloride (mmol/L)	103 (1.4)	106 (1.5)	108 (1.6)
Bicarbonate (mmol/L)	26.3 (0.4)	25.8 (0.6)	25 (0.6)
Creatinine (μmol/L)	121 (9.5)	128 (8.7)	127 (7.6)
Urea (mmol/L)	5.9 (0.5)	6.8 (0.8)	5.8 (0.6)

Values are mean ± SD.

ciency. The fluoride ion was subsequently identified as the nephrotoxic agent (8).

Serum inorganic fluoride concentrations of 50 μmol/L or more result in minor defects in urine concentrating ability, with more obvious changes occurring when inorganic fluoride concentrations are in the range of 100 μmol/L. Permanent renal damage is likely to occur only when inorganic fluoride concentrations exceed 150 μmol/L (1).

The extent of anesthetic metabolism indicates biochemical reactivity, which has implications for toxic side effects. The main pathway of isoflurane metabolism is believed to begin when an active oxygen atom is inserted into the ethyl alpha C-H bond. The resulting unstable compound is hydrolyzed to difluoromethanol and trifluoroacetic acid. Both compounds, particularly the latter, are a major source of organic fluoride (9,10). Halothane is not significantly defluorinated under normal clinical conditions; however, in the presence of hypoxia, it is metabolized through a reductive pathway, resulting in the production of fluoride ions. The principal organic metabolite of halothane is also trifluoroacetic acid.

Previous studies in humans have demonstrated that, after exposure to 3.1 MAC-hours of isoflurane during surgical procedures lasting 2.0–7.5 h, serum fluoride concentrations increased to mean peak values of about 4.4 μmol/L (11). Slightly higher peak concentrations were reported in morbidly obese patients exposed to 2.5 MAC-hours of isoflurane (12). In a series of intensive care patients who received subanesthetic concentrations of isoflurane as sedation for up to 24 h, plasma inorganic fluoride increased from a mean concentration of 4.03 to 13.57 μmol/L 12 h after the sedation was stopped (6). None of these studies demonstrated peak serum inorganic fluoride concentrations above 50 μmol/L.

Our investigation shows that after prolonged anesthesia, biotransformation of isoflurane to inorganic fluoride may result in concentrations above those that cause subclinical nephrotoxicity.

An increased metabolism of halothane to inorganic fluoride also occurs after a similar anesthetic exposure (Figure 2). However, the greatest peak fluoride concentration in the halothane group was 20.2 μmol/L, which is well below the stated nephrotoxic range. Again, in contrast to the isoflurane group, peak fluoride concentrations were maximal at 10 h; i,e, at the average end of anesthesia and surgery. This is significantly different from the isoflurane series where fluoride levels continued to increase linearly and peak at the 24-h interval, 14 h after surgery and anesthesia ended. This supports previous work that plasma concentrations of fluoride continue to rise after cessation of isoflurane anesthesia (10). It is worth noting that even though the concentrations of inorganic fluoride in this series were greater than so far reported, by 48 h they were returning toward preoperative levels. This contrasts with methoxyflurane anesthesia where peak concentrations remained elevated for 3–4 days after exposure (1,8).

Varying concentrations of inorganic fluoride are found after isoflurane administration, but these amounts are reported as being on the order of 5 μmol/L (13). The diversity of inorganic fluoride concentrations in this series may partially reflect biologic variation. None of our patients was taking medication known to increase microsomal enzyme activity. Other factors that influence microsomal enzyme activity include age, gender, obesity, and hypoxia (14). Solubility and dose of the inhaled anesthetic are also important variables to consider.

After prolonged exposure to isoflurane, anesthetic uptake and equilibrium in muscle, skin, and adipose tissue become important. Fat depots, having a large lipoid content with special affinity for anesthetics, may serve as a reservoir to provide continued delivery of drug to the liver for metabolism. This may also explain the peak increases in serum inorganic fluoride in our patients 24 h after the beginning of anesthesia.

In vivo defluorination of isoflurane has been shown to occur in hepatic microsomes. The extent of defluorination was increased by pretreatment with phenobarbitone (15). In vitro defluorination of isoflurane, enflurane, and methoxyflurane has been reported by Greenstein and colleagues (16). Linde and Berman (17) have shown that rats given hexobarbital evidenced a shortened sleeping time 24 h after a 7-h exposure to 0.3% isoflurane. This finding is also common to halothane, enflurane, and ether but not to cyclopropane or nitrous oxide. It suggests that isoflurane and other potent metabolized anesthetics themselves may induce liver enzymes. The increased metabolic capacity of liver microsomes after ether or halothane anesthesia adds support to this suggestion (17).

Recent reports have indicated that isoflurane can inhibit the oxidative metabolism of halothane (18). Wood and Wood (19) have demonstrated that halothane can significantly prolong the elimination half-life of aminopyrine for up to 24 h after anesthesia. A change in aminopyrine metabolism implies that the elimination and metabolism of other drugs could also be affected.

Isoflurane also increased the elimination half-life of aminopyrine at 2 h postoperatively but to a lesser degree than halothane. Thus prolonged anesthesia using isoflurane may result in an increase in hepatic cytochrome P450, resulting in serum fluoride levels significantly higher than have been so far reported.

It was not determined whether subclinical renal impairment occurred in either group. No significant change from baseline values was observed in serum urea, creatinine, and electrolyte concentrations postoperatively. Hourly urine volumes in the two groups were similar. The vasopressin resistance test of urinary concentrating ability (20) was not performed. It is possible, therefore, that subclinical nephrotoxicity may have existed in the group that received isoflurane.

The results of this study demonstrate that serum fluoride ion concentrations after prolonged halothane or isoflurane anesthesia increase to peak values in a linear, dose-related manner. However, after extended isoflurane administration of up to 20 MAC-hours, metabolism to inorganic fluoride may, on occasion, be of a sufficient magnitude to cause concern regarding subclinical renal dysfunction.

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Clinical Comparison of Sevoflurane and Isoflurane in Healthy Patients

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We compared blood pressure and heart rate changes in healthy patients during anesthesia with sevoflurane ($n = 50$) versus isoflurane ($n = 25$) and the rate of recovery after such anesthesia. After premedication with intravenous administration of midazolam, induction of anesthesia with thiopental, and intubation of the trachea facilitated with succinylcholine or vecuronium, anesthesia was maintained with approximately 1 MAC (sevoflurane, 2.05%; isoflurane, 1.15%) of the volatile anesthetic in oxygen for the duration of the operation. Anesthetic concentration was varied as indicated to maintain arterial blood pressure at ±20% of baseline values. Sevoflurane and isoflurane produced similar systolic and diastolic arterial blood pressures, but heart rate after incision was faster in patients given isoflurane. Recovery of response to command was shorter in patients given sevoflurane than that in patients given isoflurane (7.5 ± 0.5 min versus 18.6 ± 2.0 min). Consistent with this finding, venous blood drawn after anesthesia showed a more rapid initial decay with sevoflurane. Nausea and vomiting were comparable in both groups. We conclude that sevoflurane anesthesia, as compared with isoflurane, is associated with possible advantageous effects on heart rate and recovery.

(Anesth Analg 1992;74:241–5)

The new volatile inhaled anesthetic sevoflurane (fluoromethyl 2,2,2-trifluoro-1-[trifluoro methyl] ethyl ether) possesses a blood-gas partition coefficient of 0.6, which is lower than that of other currently used inhaled anesthetics (1). Previous animal (2–4) and early human (5) investigations indicate that sevoflurane provides a smooth anesthetic induction, rapid emergence from anesthesia, and no organotoxicity (2–4). Owing to the low blood-gas solubility, sevoflurane would be expected to provide more rapid emergence from anesthesia than currently used inhaled anesthetics would provide; however, this has not been adequately evaluated. In addition, the hemodynamic effects (arterial blood pressure and heart rate) of sevoflurane in surgical patients, compared with other inhaled anesthetics, have not been determined. In this study, we compared hemodynamic effects and emergence time in healthy surgical patients receiving either sevoflurane or isoflurane anesthesia.

Methods

After approval had been obtained from the Institutional Review Board Human Subjects Committee of the University of Arizona Health Sciences Center, 75 ASA I and II patients scheduled for elective surgical procedures were randomized in a 2 to 1 ratio to receive sevoflurane (50 patients) or isoflurane (25 patients). Written informed consent was obtained from all participants.

Patients with a medical history or physical evidence of significant hepatic or renal disease, chronic alcohol or drug abuse, significant cardiovascular disease, metastatic malignancy, or neuropsychiatric disorder were excluded from the study. A complete medical history, physical examination, electrocardiogram, and clinical laboratory studies were performed preoperatively and repeated 24 h after the anesthetic was given.

Heart rate, arterial blood pressure, and temperature were recorded before anesthesia. An intravenous infusion of 5% dextrose in lactated Ringer's solution was started. All patients received 0.01–0.03 mg/kg of midazolam administered intravenously 30 min before anesthetic induction. Preoperative arterial blood pressure (Datascope Accutorr 1A), heart

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rate, and electrocardiogram (Datascope Model 2000A) were recorded, and repeated measurements were recorded every 1 min for the first 15 min of anesthesia and then every 5 min until emergence from anesthesia. After 5 min of breathing 100% oxygen, anesthesia was induced by an intravenous injection of 3–5 mg/kg of thiopental and either 1–2 mg/kg of succinylcholine or 0.1 mg/kg of vecuronium for paralysis. Subsequent paralysis was provided by incremental doses of vecuronium, guided by peripheral nerve stimulation. Ventilation was controlled via a mask with either sevoflurane or isoflurane for 1–2 min before tracheal intubation using 2–2.5 MAC anesthetic concentrations. After endotracheal intubation, sevoflurane or isoflurane was continued in 100% oxygen using a 6 L/min oxygen flow rate; and the lungs were ventilated using a tidal volume of 10–12 mL/kg with ventilation adjusted to maintain end-tidal CO_2 concentrations between 30 and 35 mm Hg. Anesthetic gases were delivered with an Ohio Medical Anesthetic Machine (model 50) using a circle system containing Sodasorb CO_2 absorber (W.R. Grace and Co., Lexington, Mass.). End-tidal anesthetic gas concentrations were determined for both agents with a Datex multiple gas analysis monitor (model 222) modified to measure sevoflurane. This was calibrated using prepared gas standard concentrations of 1%, 2%, and 4% of the anesthetics. The vaporizers used were an Ohmeda Sevotec 3 for sevoflurane and Fortec Vaporizer for isoflurane delivery.

Initial anesthetic concentrations were 2–2.5 MAC for each anesthetic (1 MAC sevoflurane, 2.05%; 1 MAC isoflurane, 1.15%) after endotracheal intubation and were subsequently adjusted to maintain arterial blood pressure within ±20% of baseline. Oxygen flow rate was reduced from 6 L/min to 2 L/min 5 min after anesthetic induction. Sevoflurane or isoflurane concentrations were adjusted by the anesthesiologist throughout the surgical procedure to maintain minimal fluctuations of arterial blood pressure (±20%) in response to surgical stimulation. The administration of sevoflurane or isoflurane was continued at surgical anesthetic concentrations until the time of surgical wound closure. Paralysis was reversed using intravenous neostigmine with glycopyrrolate and monitored with train-of-four ratios. End-tidal anesthetic gas concentrations were then recorded, and maintenance anesthetic administration was discontinued. Oxygen flow rate was then increased to 6 L/min and controlled ventilation was continued for 1 min with spontaneous ventilation subsequently allowed to return. The endotracheal tube remained in place with the patient breathing spontaneously. The response time to the command "open your eyes" was recorded by a research nurse assistant who was not blinded to the anesthetic used.

Table 1. Patient Characteristics

	Sevoflurane	Isoflurane
n	49	25
Age (yr)	41.9 ± 1.9	41.5 ± 2.5
Height (cm)	165.2 ± 1.4	164.0 ± 2.2
Weight (kg)	70.9 ± 1.8	66.2 ± 2.4
Body mass index	26.0 ± 0.8	24.5 ± 0.9

Values are mean ± SEM. No significant differences exist between sevoflurane and isoflurane groups in any category.

After eye opening to command, the trachea was extubated, and the patient was transferred to the postanesthetic care unit (PACU). No narcotics or benzodiazepines were administered before eye opening on command. Narcotics were administered after tracheal extubation when the patient exhibited or vocalized discomfort. The incidence of nausea and vomiting was monitored by a research nurse during the PACU time period. The incidence of complaints of nausea and vomiting was recorded on the ward by the nursing staff.

Blood samples (1 mL each) were obtained from patients through a heparin-flushed venous arm catheter for analysis of sevoflurane or isoflurane anesthetic concentration in the blood every 30 min during anesthesia, at anesthesia end, and then at 15, 30, 45, 60, 90, 120, 180, 480, and 1440 min after anesthesia. The anesthetic concentration in the blood was analyzed by *n*-heptane extraction and by subsequent gas chromatography (6).

Hemodynamic data were analyzed using repeated-measures analysis of variance with Student's *t*-test where appropriate. Patient demographics were compared using Student's *t*-test. χ^2-Analysis was used to compare incidence of postoperative nausea between groups. Anesthetic concentrations in the blood were compared between groups using Student's *t*-test.

Results

Of the 75 patients enrolled in the study, 74 were included for analysis. Results from one patient anesthetized with sevoflurane were excluded owing to a neurologic disorder unrecognized before anesthesia and surgery. (This patient had an emergence time of 39 min after administration of sevoflurane anesthesia.)

The two patient groups did not differ in age, height, or weight (Table 1). The types of surgery for each anesthetic group and average ASA classification are also listed in Table 1.

The systolic and diastolic arterial blood pressures increased compared with baseline values 1 min after tracheal intubation in the both sevoflurane and isoflurane groups. At 5 min after tracheal intubation,

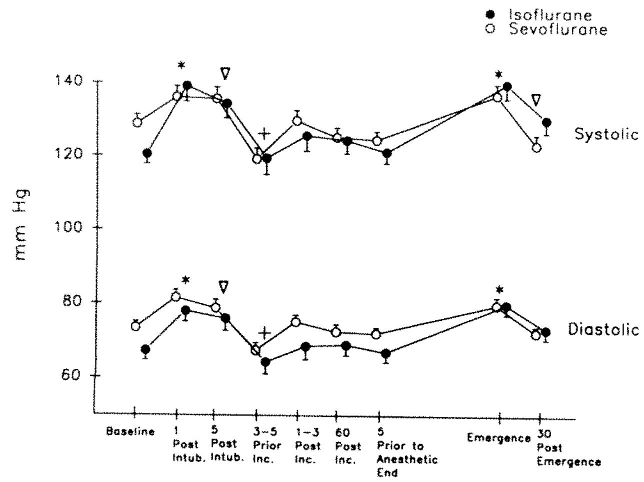

Figure 1. Systemic systolic and diastolic arterial blood pressure changes during sevoflurane and isoflurane surgical anesthesia. *Differs from baseline blood pressure values for both sevoflurane and isoflurane groups, $P < 0.05$. $^{\nabla}$Differs from baseline blood pressure value in isoflurane group only, $P < 0.05$. †Differs from baseline blood pressure value in sevoflurane group only, $P < 0.05$. Data shown as mean ± SEM. Intub, intubation; Inc, incision.

systolic and diastolic arterial blood pressures were higher than baseline values in only the isoflurane group (Figure 1). Compared with baseline values, sevoflurane anesthesia decreased systolic and diastolic arterial blood pressures 3–5 min before surgical incision, whereas in the isoflurane group, systolic and diastolic arterial blood pressures did not differ from baseline values at this time. Arterial blood pressures did not differ from baseline values after incision or during maintenance anesthesia with sevoflurane and isoflurane but increased in both groups during emergence from anesthesia. Baseline systolic arterial blood pressure values for the sevoflurane group were greater than those for the isoflurane group, hindering direct comparison; however, baseline diastolic blood pressure values did not differ and a comparison of values at all time points analyzed did not show a difference between sevoflurane and isoflurane groups.

Heart rate was significantly more rapid in the isoflurane group when compared with the sevoflurane group at three analyzed time points (3–5 min before incision, 1–3 min after incision, and 1 h after surgical incision) (Figure 2). Heart rate was more rapid at 5 min before anesthetic end and during emergence from anesthesia than at baseline in the isoflurane-anesthetized group only. Heart rate decreased after anesthesia emergence in both groups in the PACU after narcotic administration. Baseline heart rate values did not differ between sevoflurane and isoflurane groups.

Emergence from anesthesia determined by eye opening to command was faster with sevoflurane than with isoflurane ($P < 0.001$). The mean emergence time for the sevoflurane group was 7.5 ± 0.5 min and for the isoflurane group, 18.6 ± 2.0 min. The duration of anesthetic exposure to sevoflurane in MAC hours did not differ between anesthetic groups (Table 2). The mean end-tidal anesthetic concentration for the sevoflurane group at the end of anesthesia was 2.1% ± 0.06% and for the isoflurane group, 1.3% ± 0.07%. The MAC values at the end of anesthesia for sevoflurane (1.04 ± 0.21) compared with isoflurane (1.13 ± 0.41) did not significantly differ. The time to recovery from anesthesia (minutes) did not correlate with MAC hours of sevoflurane anesthesia. A positive correlation did exist for the relationship between anesthetic dose (MAC hours) and emergence time after isoflurane anesthesia ($r = 0.57$, $P < 0.01$) (Figure 3). The decrease of anesthetic

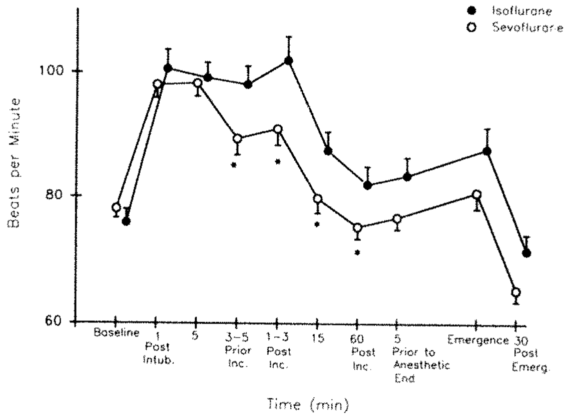

Figure 2. Heart rate changes during sevoflurane and isoflurane surgical anesthesia. *Differs significantly from isoflurane values. $P < 0.05$. Data shown as mean ± SEM. Intub, intubation; Inc, incision; Emerg, emergence.

Table 2. Anesthetic Duration and Postanesthetic Data

	Sevoflurane	Isoflurane
MAC hours (h)	2.5 ± 1.1	2.7 ± 1.2
Emergence time (min)	7.5 ± 0.5^a	18.6 ± 2.0
Narcotic administration time (min)	11.8 ± 0.7^a	22.4 ± 2.2
Incidence of nausea in PACU (% of patients)	5/49 (10%)	3/25 (12%)
Incidence of emesis in PACU (% of patients)	0/49 (0%)	0/25 (0%)
Incidence of nausea after PACU (first 24 h) (% of patients)	17/49 (34%)	11/25 (44%)
Incidence of emesis after PACU (first 24 h) (% of patients)	1/49 (2%)	2/25 (8%)

Emergence time = time to eye opening on command after anesthetic discontinuation; narcotic administration time = time at which any narcotics were administered after anesthetic discontinuation; nausea or emesis after PACU = percent of patients having nausea or emesis within the first 24 h after discharge from the PACU.

^{a}Significantly differs from isoflurane group, $P < 0.001$.

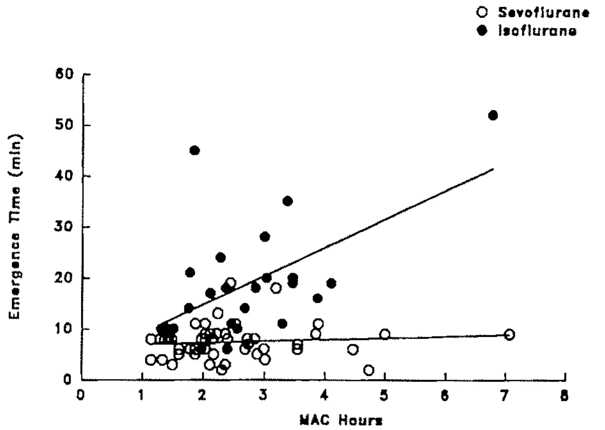

Figure 3. Correlation between individual anesthetic emergence times and duration of anesthetic exposure (MAC hours). A positive correlation is present for isoflurane $r = 0.57$ ($y = 5.56x + 3.67$) but not sevoflurane $r = 0.10$ ($y = 0.31x + 6.69$).

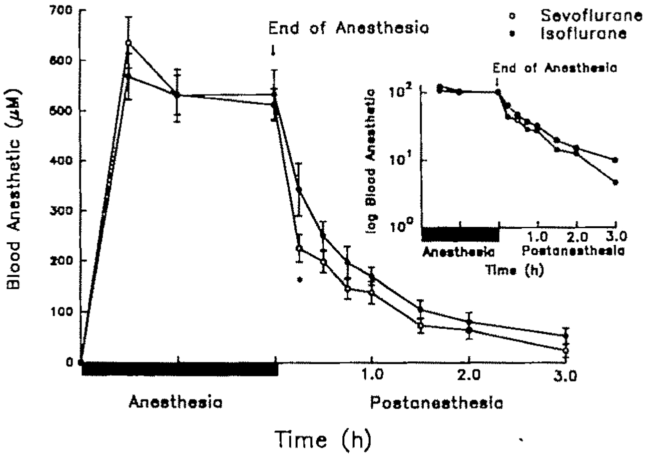

Figure 4. Sevoflurane and isoflurane anesthetic concentrations in the venous blood during and after anesthesia. Data shown as mean ± SEM. Sevoflurane, $n = 30$. Isoflurane, $n = 24$. *Differs significantly from isoflurane value, $P < 0.05$. *Inset:* shows the same anesthetic concentrations in semilogarithmic plot.

concentration in venous blood was faster with sevoflurane than with isoflurane. Fifteen minutes after anesthetic discontinuation, the sevoflurane concentration in the blood was significantly lower than that of isoflurane (Figure 4). Intravenous narcotic administration after anesthetic discontinuation was required sooner with sevoflurane than with isoflurane (11.8 ± 0.7 vs 22.4 ± 2.2 min).

The incidence of postoperative nausea and vomiting occurring in the PACU or in the ward within the first 24 h after anesthesia did not differ between sevoflurane- and isoflurane-anesthetized groups (Table 2).

Discussion

Cardiovascular variables were well maintained with sevoflurane. Systemic systolic and diastolic arterial blood pressures were not significantly different from those occurring in the isoflurane-anesthetized group. Sevoflurane in animal studies has been shown to either reduce (7,8) systemic vascular resistance or maintain it (9) depending on the animal species evaluated. Changes in cardiac output are generally comparable to those produced with isoflurane (7,8). During relatively stable surgical anesthesia conditions obtained 1 h after the surgical incision, values of systolic and diastolic arterial blood pressure in both groups were not different from baseline values. However, conclusions regarding equianesthetic concentration effects of the anesthetics cannot be made as each drug was titrated against the arterial blood pressure.

Heart rate before and after surgical incision with sevoflurane was lower than that with isoflurane, perhaps because of the more rapid equilibration of sevoflurane as anesthetic concentrations were increased in response to hemodynamic changes after tracheal intubation. More rapid equilibration appeared to allow more rapid adjustment of anesthetic depth after a change in delivered anesthetic concentration. In addition, sevoflurane may not produce the tachycardia sometimes noted with isoflurane. Studies in animals (7,9) and humans (5) have shown that sevoflurane does not produce tachycardia; however, one study in dogs found that heart rate increases were larger with sevoflurane than with isoflurane (8). During isoflurane anesthesia, tachycardia may also be better controlled with the concomitant use of narcotic anesthetics (10) not used during anesthesia in our study.

The incidence of postoperative nausea did not differ between the sevoflurane and isoflurane groups, with an incidence of 10% and 12%, respectively, occurring in the PACU immediately after anesthesia (Table 2). All patients complaining of nausea received droperidol (1.25 mg IV). No patient in either group had emesis occur in the postanesthetic care unit. The incidence of nausea and emesis after the patient's transfer to the ward within the first 24 h also did not differ between anesthetic groups. All patients in our study received parenteral narcotics during recovery and on the ward, with many of them receiving patient-controlled analgesia that may have influenced the incidence of nausea in both anesthetic groups. Sevoflurane's lack of an increased propensity to produce nausea combined with its ability to provide a rapid emergence may make it an attractive outpatient inhaled anesthetic.

One patient was eliminated from the study owing to a history of Huntington's chorea, the severity of which was not disclosed preoperatively. This patient required 39 min to emerge from sevoflurane anesthesia. This duration of emergence was 20 min longer than any other patient in the sevoflurane group. It is possible that the prolonged emergence was due to the use of a barbiturate previously reported to produce prolonged emergence in patients with this disease (11).

The blood-gas solubility coefficient of sevoflurane (0.6) is lower than that of either isoflurane or other currently used volatile inhaled anesthetics. This property of sevoflurane should allow a more rapid induction of anesthesia and emergence in comparison with that of other volatile anesthetics. Anesthetic inhalation induction time was not evaluated in this study. However, other investigations have confirmed that anesthetic induction with sevoflurane is both smoother and more rapid than with other currently used inhaled anesthetics (5,12). Emergence after sevoflurane anesthesia occurs more rapidly than with other currently used inhaled anesthetics in animal studies (9,13). Most investigations in humans have reported a rapid emergence with sevoflurane, although one investigation found emergence from sevoflurane anesthesia to be no more rapid than emergence from enflurane anesthesia (12). Saito et al. hypothesized that the more comparable brain-blood partition coefficients of these two anesthetics may have been responsible for their results. We found a more rapid emergence occurred after sevoflurane anesthesia (7.5 min) compared with isoflurane anesthesia (18.6 min). Additionally, there was positive duration and emergence time with isoflurane as shown in Figure 3. This correlation did not exist after sevoflurane anesthesia, suggesting that anesthetic duration did not affect the more rapid emergence occurring with this anesthetic.

The more rapid emergence with sevoflurane was also supported by the more rapid decrease in anesthetic concentration in the blood that occurred primarily during the very early period after anesthetic discontinuation. Fifteen minutes after anesthesia, sevoflurane concentrations in the blood were approximately two-thirds those of isoflurane. This early rapid decrease is consistent with the low blood-gas solubility coefficient of sevoflurane. A decrease in anesthetic concentrations in the blood at later time points may show less difference between sevoflurane and isoflurane owing to similar transfer between other tissue compartments.

Of particular importance was our methodology for anesthetic delivery before discontinuation of anesthesia. At the termination of the operation and anesthesia, the anesthetic concentration is commonly reduced to provide more rapid emergence. However, to provide a consistent anesthetic depth from which to measure anesthetic emergence, we chose to continue an anesthesia level required for hemodynamics control during operation until the final skin suture was placed, at which time the anesthetic was discontinued and emergence began. In addition, the use of nitrous oxide in combination with the volatile inhaled anesthetics may reduce the difference in emergence times between the anesthetic agents. Therefore, our results for emergence time of the two anesthetics studied can certainly be improved by techniques used in routine clinical practice.

In summary, we found sevoflurane to provide lower heart rate values before and after surgical incision during anesthetic maintenance compared with isoflurane. A much more rapid emergence was provided after anesthetic discontinuation of sevoflurane compared with isoflurane. These properties of sevoflurane would appear to afford this anesthetic potential advantage over other currently used inhaled anesthetics.

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Lidocaine for the Prevention of Pain Due to Injection of Propofol

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Propofol has a high incidence of pain with injection, particularly into small veins. We sought to determine whether concomitant administration of lidocaine could prevent this pain. In a randomized double-blind trial, 368 women were allocated to one of four groups to receive 19 mL of propofol mixed with either 1 mL of 0.9% saline, 1 mL of 0.5% (5 mg) lidocaine, 1 mL of 1% (10 mg) lidocaine, or 1 mL of 2% (20 mg) lidocaine. The pain of injection was scored as none, mild, moderate, or severe. There was a significant reduction in the overall incidence of pain from 73% with saline to 32% with 20 mg of lidocaine. A highly significant negative dose-response relationship between the dose of lidocaine and the severity of pain was demonstrable, both at induction of anesthesia and as recalled in the recovery room ($P < 0.001$ for both). Lidocaine (20 mg IV) will significantly reduce the incidence and severity of pain with propofol injection, but about 6% of patients will still suffer unpleasant pain if the dorsum of the hand is used.

(Anesth Analg 1992;74:246–9)

The incidence of pain from injection of propofol (1) ranges from 25% to 100% if a vein on the dorsum of the hand is used (2–10) and less (3%–36%) if injected into larger proximal veins, e.g., at the antecubital fossa (4,7,11). The sensation produced is usually described as tingling, cold, or numbing or, at its worst, a severe burning pain proximal to the site of injection. This sensation tends to occur within 10–20 s of injection and lasts only for the duration of the injection. Despite this discomfort, the incidence of venous sequelae, such as phlebitis, is less than 1% (2,12).

A single dose of 1 mL of 1% lidocaine mixed with 19 mL of propofol (a dose arbitrarily chosen by Brooker et al. [3] in a pilot study) reduced pain on injection in several small studies (7,8,13–15). The aim of our study was to determine the dose-response relationship for the addition of lidocaine to propofol in reducing the pain of injection.

Methods

The study was approved by the Canterbury Area Health Board Ethical Committee. Four hundred fit, healthy women (ASA physical status I or II) undergoing minor gynecologic operations were studied after they gave informed, written consent. Thirty-two patients were subsequently excluded because of incomplete data, leaving 368 patients for analysis (Table 1). All were unpremedicated and had a luered 20-gauge Jelco cannula inserted into a vein on the dorsum of the hand. The cannula was flushed with normal saline. No other injectate was used before the induction of anesthesia with propofol. Patients were randomized in a double-blind manner to receive 1 mL of either 0.9% saline, 0.5% (5 mg) lidocaine, 1% (10 mg) lidocaine, or 2% (20 mg) lidocaine mixed with 19 mL of propofol (10 mg/mL). Approximately 2 mg/kg of propofol was injected at a rate of 0.5–1 mL/s for induction of anesthesia.

Midway through the injection of propofol and before they became drowsy, the patients were asked "Is your arm comfortable?" If the reply was "No," then the patients were asked to grade the pain as mild, moderate, or severe. After recovering from anesthesia, patients were asked by one of three recovery room nurses whether they had any recall of the injection, whether it was painful, and if so, again

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Table 1. Demographic Data for 368 Patients Studied

		Lidocaine		
	Saline	5 mg	10 mg	20 mg
No. of patients	98	90	90	89
Age (yr)	31 ± 10	31 ± 10	33 ± 10	31 ± 10
Body weight (kg)	61 ± 11	63 ± 11	66 ± 12	64 ± 11

Values are mean ± SD.
There were no significant differences between treatment groups.

Table 2. Incidence of Pain Reported at the Time of Induction of Anesthesia

		Lidocaine		
Induction pain	Saline ($n = 98$)	5 mg ($n = 91$)	10 mg ($n = 90$)	20 mg ($n = 89$)
None	26 (27)	45 (49)	61 (67)	61 (68)
Mild	21 (21)	25 (28)	14 (16)	18 (20)
Moderate	19 (19)	13 (14)	7 (8)	5 (6)
Severe	32 (33)	8 (9)	8 (9)	5 (6)

Numbers in parentheses are percents.
Linear test for trend $\chi^2 = 40.9$, $P < 0.0001$; Gamma correlation − 0.45, $P < 0.001$.

Table 3. Incidence of Pain as Recalled in the Recovery Period

		Lidocaine		
Recall of pain	Saline ($n = 97$)	5 mg ($n = 91$)	10 mg ($n = 88$)	20 mg ($n = 88$)
None	29 (30)	52 (57)	59 (67)	68 (77)
Mild	14 (14)	11 (12)	9 (10)	8 (9)
Moderate	27 (28)	18 (20)	10 (11.5)	8 (9)
Severe	23 (24)	5 (5.5)	7 (8)	2 (2.5)
No recall	4 (4)	5 (5.5)	3 (3.5)	2 (2.5)

Numbers in parentheses are percents.
Linear test for trend $\chi^2 = 39.4$, $P < 0.0001$; Gamma correlation − 0.48, $P < 0.001$.

to grade it as mild, moderate, or severe. All patients were questioned in an identical manner.

Previous studies reported an incidence of pain of 40% and 15% for placebo and lidocaine, respectively. One hundred patients were planned for each treatment to detect such a difference with power of 95%, with $\alpha_2 = 0.05$. The data were analyzed on a DEC microVax computer using a biomedical statistical package (16). The statistical significance of differences between groups was tested by the χ^2 test. A probability level of less than 5% was accepted as significant. A linear trend with dose was tested using a 2 × 4 contingency table with pain grouped as none/mild or moderate/severe. The index of correlation between the four doses of lidocaine and the amount of pain was estimated using the Goodman-Kruskal gamma coefficient (17).

Results

The groups were similar in age and body weight (Table 1). Lidocaine significantly reduced the incidence and severity of pain during induction of anesthesia as reported both at the time and as recalled in the recovery period ($\chi^2 = 64.8$ and 58.5, respectively; df = 3, $P < 0.0001$ for both). The frequencies reported in the four groups are shown in Tables 2 and 3.

Injection of propofol without lidocaine caused pain in 73% of the patients, with 32% complaining of severe pain. Almost 50% of the pain reduction occurred with the use of 5 mg of lidocaine, particularly in the severe category. However, the incidence of pain was further reduced with larger doses of lidocaine, the addition of 20 mg of lidocaine reducing the incidence of pain to a minimum of 31% with only 5.6% complaining of severe pain. A highly significant negative dose-response relationship was found between the amount of lidocaine and the incidence of pain reported both during induction of anesthesia and as recalled in recovery (linear test for trend, $\chi^2 = 40.9$ and 39.4, respectively, $P < 0.0001$ for both; gamma correlation = −0.45 at induction and −0.48 on recall, $P < 0.001$ for both).

Discussion

The quality of an anesthetic as judged by the patient is clearly influenced by any recall of discomfort or pain at the time of anesthetic induction. Interestingly, Hynynen et al. (5) concluded that the high incidence of severe pain experienced by their patients with injection of propofol made it a drug unlikely to gain popularity for routine clinical use.

The cause of the pain on injection of propofol is unknown but may be due to the activation of pain mediators such as kininogens (7). Many measures have been tested empirically to reduce the pain. Slowing the speed of injection increases discomfort (7), and premedication with benzodiazepines, opiates, or phenothiazines is not clearly of benefit (18–20). The prior intravenous administration of aspirin may reduce the pain with propofol (21).

Although injection into a larger proximal vein causes less pain than a more distal injection, implying that dilution should help, the benefits of preinjection dilution of propofol or injection into a fast-running infusion are controversial (5–7,22). Refrigerating propofol to 4°C also reduces pain without reducing its efficacy as an anesthetic (9).

Pretreatment with intravenous lidocaine decreased pain on injection with methohexitone (12,23) but not with propofol (3,4). A venous tourniquet (with 1 mL of 1% lidocaine injected distally) not released until the injection of propofol 2 min later was of no benefit (7), whereas 20 and 40 mg of lidocaine with the venous occlusion released at 20 s did decrease pain (10).

A recent French study (11), of similar design to this one, used veins in the anticubital fossa and noted a reduction in pain from 36% to 15% with the addition of 0.1 mg/kg of lidocaine, but there was no additional benefit from 0.2 or 0.4 mg/kg of lidocaine. In our study, there was also a significant reduction in the incidence of pain with all doses of lidocaine compared with saline. In addition, a strong negative dose-response relationship was demonstrated over the range 0–20 mg. This difference in dose-dependent effect between the two studies is most likely due to the site of injection, large proximal veins versus smaller distal vessels.

Even with 20 mg of lidocaine, 6% of the patients complained of unpleasant pain. There may be a subgroup of patients who, despite all measures, will still experience severe pain. Anecdotally, it seems to be patients with Raynaud-type symptoms. This may be a group worth studying, particularly in trying to elucidate the etiology of venous pain. The anesthetist should be prepared to use another anesthetic known to have a lower incidence of pain on injection, e.g., thiopental, under these circumstances or avoid veins on the dorsum of the hand.

The addition of lidocaine to the propofol in the same syringe is a simple, safe technique (8). It should be mixed with propofol within 30 min of use to ensure a stable emulsion. Otherwise, lidocaine moves into the lipid phase, progressively decreasing the free effective concentration of propofol.

The best way of measuring pain in the clinical setting is by verbal response or its derivative, the visual analogue scale (VAS) (24,25). The VAS appears to be more sensitive to smaller changes in effect over time than are categorical measures (24). A four-point verbal categorical scoring system was chosen in this study rather than a VAS for four reasons. First, it is simple to apply and readily understood by patients. Second, all the previous studies reporting pain on injection of propofol have used either all-or-none or categorical scoring systems, thus allowing easier comparison with the literature. Third, there is little evidence that a VAS would enhance the numerical interpretation of a single subjective report of transient pain. Finally, we were concerned that the appropriate hand-eye coordination required for a VAS might not be present in all patients during the rapidly changing state of consciousness of anesthesia induction, resulting in a significant loss of data.

There was satisfactory internal consistency in pain scoring despite the use of a four-point categorical scale. Although there was a slight tendency for patients to underreport pain when asked to recall the induction, there remained a strong correlation between pain scores as reported on the two occasions ($\chi^2 = 460.1$; $P < 0.0001$). Therefore, a comfortable induction of anesthesia is important as most patients will have a clear recollection of these events. Interestingly, 4% of the patients had no recall of the injection despite not receiving any prior medication. Most of these patients did not experience pain. Propofol is not thought to have retrograde amnesic properties, and it is unlikely to be due to lidocaine as lack of recall occurred with similar frequencies in all four groups.

This study confirms the efficacy of lidocaine in reducing the incidence and severity of pain on injection of propofol. A dose-response relationship was demonstrated over the range 0–20 mg of lidocaine, supporting the use of 20 mg of lidocaine added to a 20-mL ampule of propofol immediately before injection to minimize discomfort.

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Tourniquet at 50 mm Hg Followed by Intravenous Lidocaine Diminishes Hand Pain Associated With Propofol Injection

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We evaluated the efficacy of intravenous lidocaine, with and without a tourniquet, to decrease the intensity of pain during intravenous propofol injection in 82 patients undergoing general anesthesia. Patients in group A ($n = 20$) received propofol (2 mg/kg IV); patients in group B ($n = 22$) received 2% lidocaine (100 mg IV) followed 1 min later by propofol (2 mg/kg). Patients in group C ($n = 21$, saline placebo) and D ($n = 19$, 2% lidocaine) had an arm tourniquet inflated to 50 mm Hg applied for 1 min after gravity drainage of venous blood. The intensity of pain along the forearm was marked on a 0–100-mm visual analogue scale. Pain intensity was less in group B (21 ± 19 mm) than in group A (75 ± 28 mm; $P < 0.05$). Pain intensity was significantly less in group D (1 ± 2 mm) compared with group B (21 ± 19 mm; $P < 0.001$). We conclude that intravenous lidocaine before propofol injection attenuates the painful response; whereas, lidocaine administered after a tourniquet inflated to 50 mm Hg for 1 min virtually abolishes the pain associated with intravenous propofol.

(Anesth Analg 1992;74:250–2)

Propofol is given intravenously for the induction and maintenance of anesthesia. It possesses many characteristics of an ideal anesthetic and produces hypnosis rapidly with minimal excitation during one arm-to-brain circulation (1–3). One of the most notable side effects of propofol is pain during an intravenous injection. Lidocaine pretreatment has been proposed to decrease injection-related pain, but its effectiveness is unclear (4–15).

We evaluated the efficacy of lidocaine, with and without a tourniquet applied to the arm, in decreasing the intensity of pain during propofol injection.

Methods

Eighty-two adult patients (ASA physical status I or II) undergoing elective surgery under general anesthesia were randomly assigned by computer to one of four groups. The study was approved by the Institutional Human Research Committee, and informed consent was obtained from each patient.

Patients in group A ($n = 20$) received propofol (2 mg/kg IV); those in group B ($n = 22$) were given 2% lidocaine (5 mL) IV followed 1 minute later by propofol (2 mg/kg). Patients in group C ($n = 21$) and D ($n = 19$) had an arm tourniquet inflated to 50 mm Hg applied after 30 s of gravity drainage of venous blood, followed by the administration of a saline placebo (5 mL) (group C) or 2% lidocaine (5 mL) (group D). The tourniquet was released 1 min later, followed by intravenous injection of 2 mg/kg of propofol.

Premedication was omitted. No patient experienced any symptoms from 100 mg of lidocaine. Crystalloids were administered at a rate of 125 mL/h. An 18-gauge angiocatheter was inserted in a hand vein without subcutaneous lidocaine infiltration. All medications were delivered through the injection port nearest the catheter. Patients rated the intensity of pain along the forearm during propofol administration by marking a line on a 0–100-mm visual analogue scale (VAS). Estimated time for completion of the VAS was approximately 5 s and an estimated 35 s before the advent of hypnosis. Data were summarized as mean ± standard deviation. A statistical comparison of VAS scores was made with an analysis of variance, χ^2, and Newman-Keuls test (16). Nonparametric data were statistically evaluated with

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Table 1. Incidence of Pain Among the Four Patient Groups

Patient group	*n*	VAS (mm)	VAS >0 (%)
A	20	75 ± 28	90 (18/20)
B	22	21 ± 19	91 (20/22)
C	21	43 ± 26	86 (18/21)
D	19	1 ± 2[a]	37 (7/19)[b]

VAS, visual analogue scale.

[a] $P < 0.01$ (group D compared with groups A, B, and C) for incidence of pain.

[b] $P < 0.0001$ (group D compared with groups A and B) for intensity of pain.

Kruskal-Wallis tests. A probability value of less than or equal to 0.05 was considered significant.

Results

There were 35 women and 47 men studied. There were 32 patients with infusion sites in the right hand and 50 patients with infusion sites in the left hand. The total average age of patients in all groups was 37 ± 12 yr. No significant differences in sex, age, or ASA classification existed among the groups. The incidence of pain (VAS > 0) was 90% (18/20) in group A, 91% (20/22) in group B, 86% (18/21) in group C, and 37% (7/19) in group D (Table 1). χ^2 Analysis, which compared group A (no lidocaine), group B (lidocaine without a tourniquet), and group C (placebo) with group D (lidocaine with a tourniquet), for more burning was statistically significant ($P < 0.01$) with respect to the incidence of pain. Group A patients had a VAS of 75 ± 28 mm; group B a VAS of 21 ± 19 mm; group C a VAS of 43 ± 36 mm, and group D a VAS of 1 ± 2 mm. Pain intensity was significantly less in patients who received lidocaine before propofol (group B; 21 ± 19 mm) than in the control group (group A; 73 ± 28 mm, $P < 0.05$). Pain intensity was significantly less in patients receiving lidocaine with a tourniquet (group D; 1 ± 2 mm) compared with those receiving lidocaine without a tourniquet (group B; 21 ± 19 mm), and those receiving only propofol (group A; 75 ± 28 mm) ($P < 0.0001$). The tourniquet with placebo (group C; 43 ± 36 mm) did not decrease the pain significantly, although the pain level was less than group A where no placebo or tourniquet was used ($P < 0.05$).

Discussion

Recommendations for the elimination of pain caused by propofol on injection include rapid rate of injection (4), using larger veins (4,5), pretreatment with narcotics (5–7), diluting the propofol emulsion (8,9), cooling it before the injection (10), and pretreatment and mixing with lidocaine (4,7,11). Propofol (2:6 di-isopropyl phenol), formulated in a white, oil-in-water emulsion, caused pain by local irritation when given intravenously in the dorsum of the hand.

The manufacturer advises that transient local pain may occur during intravenous injection, which may be reduced by prior injection of intravenous lidocaine (1 mL of 1% solution). The effectiveness of intravenous lidocaine premedication is unclear (4–15). Studies have addressed this issue, and their results do not agree. Johnson et al. (11) and Morton (12) found that pretreatment with lidocaine was effective in decreasing but not eliminating the pain on injection. Conversely, McCulloch and Lees (13) and Brooker et al. (7) in similar studies did not find lidocaine pretreatment effective in decreasing the incidence of transient local pain associated with intravenous propofol injection. Ewart and Whitwam (14) studied the frequency of pain after propofol injection with 20 mg of lidocaine and concluded that lidocaine is effective in the reduction of pain when immediately given before propofol. They found less pain if propofol is given within 10 s after the lidocaine. The results of these studies are confusing, as lidocaine dosages were not standardized and methods of pain assessment were not discussed.

In our investigation, we used a tourniquet inflated to 50 mm Hg of pressure above systolic, followed by 100 mg (5 mL) of lidocaine. After waiting for 1 min, anesthesia was induced and the pain was abolished in all group D patients ($n = 19$) with a VAS of 1 ± 2 mm. Both the manufacturer and Porteous (15) recommended holding a finger over the vein for 15–60 s after 1 mL (20 mg) of lidocaine was administered. We have found this to be unpredictable and unreliable in alleviating the pain.

When the patient enters the operating room, a rubber tourniquet is placed on the same arm as the intravenous line, and 100 mg (5 mL) of lidocaine is given. The anesthesiologist then can proceed to place the standard monitors. At the end of 1 min, the tourniquet is removed, and induction of anesthesia is started with minimal burning. These patients can be compared with group D patients with a VAS of 1 ± 2 mm. In comparison, patients in groups A, B, and C experienced significant burning, albeit less in group B (VAS 21 ± 19 mm). The free flow of lidocaine (group B) provided some but not enough analgesia to predictably prevent burning. Consequently, with a tourniquet inflated and the lidocaine held in the vein for 1 min, thereby anesthetizing the vein, a modified Bier block is performed.

We conclude that intravenous lidocaine administration before propofol injection attenuates the painful response; whereas, lidocaine administered after a tourniquet is inflated to 50 mm Hg virtually abolishes the transient local pain associated with propofol injection. Larger doses of lidocaine are very effective as noted by Morton (12). This simple, readily available technique eliminated the unpleasant side effect of pain, allowed for a more tolerable induction of anesthesia, and increased patients' acceptance of propofol.

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Comparison of Induction, Maintenance, and Recovery Characteristics of Sevoflurane-N_2O and Propofol-Sevoflurane-N_2O With Propofol-Isoflurane-N_2O Anesthesia

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Induction of, maintenance of, and recovery from sevoflurane anesthesia were compared with propofol and isoflurane anesthesia when administered with nitrous oxide to patients undergoing gynecologic surgery. Seventy-five healthy (ASA I or II), consenting patients were randomly assigned to receive either (I) propofol for induction of anesthesia and isoflurane-nitrous oxide for maintenance (control), (II) propofol for induction and sevoflurane-nitrous oxide for maintenance, or (III) sevoflurane-nitrous oxide for induction and maintenance of anesthesia. Inhaled induction of anesthesia with sevoflurane-nitrous oxide was rapid (109 ± 25 s to loss of consciousness) and without any untoward hemodynamic changes or episodes of coughing and laryngospasm. Mean arterial blood pressure after induction of anesthesia with propofol (71 ± 11, 73 ± 12 mm Hg for groups I and II, respectively) was lower than when sevoflurane (80 ± 14 mm Hg) was used. The emergence time after discontinuation of isoflurane-nitrous oxide (6.7 ± 2.2 min) was significantly longer than after propofol-sevoflurane-nitrous oxide or sevoflurane-nitrous oxide alone (4.1 ± 2.2 and 4.0 ± 2.0 min for groups II and III, respectively). However, later recovery events did not differ between groups. Serum fluoride levels increased after administration of sevoflurane but not isoflurane. The levels of fluoride ions correlated with the degree of exposure to sevoflurane in MAC-hours. In conclusion, induction of anesthesia with either propofol or sevoflurane-nitrous oxide was rapid and without significant side effects. Emergence and early recovery after maintenance of anesthesia with sevoflurane-nitrous oxide was significantly faster than that after an isoflurane-nitrous oxide combination.

(Anesth Analg 1992;74:253–9)

Sevoflurane, a methyl-isopropyl ether, has a low blood-gas partition coefficient of 0.69 (1). This low solubility should contribute to a more rapid induction of, and emergence from, anesthesia than is possible with existing volatile anesthetics. Of those in current clinical use in North America, isoflurane has the lowest blood-gas solubility at 1.46 (2).

The objective of this study was to compare the induction, maintenance, and recovery profiles after general anesthesia with sevoflurane and nitrous oxide alone or after propofol, to a standard anesthetic technique consisting of propofol, isoflurane, and nitrous oxide in patients undergoing major gynecologic procedures. Fluoride levels were measured during the perioperative period to assess sevoflurane's potential for renal toxicity.

Methods

Seventy-five, ASA physical status I or II women, aged 21–69 yr, scheduled for elective gynecologic procedures (e.g., hysterectomy) were studied according to a protocol approved by the Washington University Human Studies Committee. After obtaining written informed consent, patients were randomly assigned to one of three anesthetic treatment groups using an open (nonblinded) study design. Patients with a history of hypersensitivity to halogenated anesthetics, or taking drugs and/or medications known to influence anesthetic or analgesic requirements, were excluded. Patients who had received a general anesthetic within the 7-day period before the study were also excluded. Finally, all patients of childbearing potential, as well as those with clinically significant cardiovascular, pulmonary, renal, or hepatic disease, were excluded.

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No preanesthetic medications were administered. After placement of an intravenous cannula, 10 mL of blood was withdrawn into a plastic container for measurement of baseline (preoperative) serum levels of fluoride ions using an ion-selective electrode (Smith-Kline Laboratories, Van Nuys, Calif.). The lower limit of detection was 5 μmol/L, with an assay variability of ±10%. All patients breathed 100% oxygen for 2–3 min before induction of anesthesia. After administering fentanyl (1.5 μg/kg IV), lidocaine (50 mg IV), and *d*-tubocurarine (2–3 mg IV), anesthesia was induced with either propofol or sevoflurane with nitrous oxide.

In groups I and II, anesthesia was induced with propofol (2.0 mg/kg IV) administered over 10–15 s. In group III, anesthesia was induced by inhalation of sevoflurane with nitrous oxide, 60% in oxygen, with a total gas flow of 5 L/min. Sevoflurane was delivered using a Sevotec III vaporizer (Ohmeda, Madison, Wis.) at an inspired concentration of 5% with nitrous oxide, 60% in oxygen, from the outset of anesthetic induction. The end-tidal concentration of sevoflurane was continuously monitored by Laser-Raman spectroscopy (RASCAL, Ohmeda). The calibration of this gas analyzer was checked before each surgical procedure using gases analyzed to ±0.01% accuracy (Scott Medical Products, Plumsteadville, Pa.). The end-tidal concentration of sevoflurane at the time the patients failed to respond to verbal commands and the time from the start of sevoflurane administration to unconsciousness (i.e., failure to respond to eyelash stimulation) were recorded. The occurrence of pain from injection of intravenous medication, excitatory phenomena (e.g., moving, myoclonus), respiratory problems (e.g., coughing, breathholding, apnea, laryngospasm, bronchospasm), and other adverse effects were recorded. In all three groups, intubation of the trachea was facilitated with succinylcholine (1.5 mg/kg IV), which was administered after loss of consciousness.

In group I, anesthesia was maintained with isoflurane and nitrous oxide, 60% in oxygen, and in groups II and III with sevoflurane in nitrous oxide, 60% in oxygen. The inspired concentration of the volatile anesthetic was adjusted as necessary to maintain the mean arterial blood pressure and heart rate within 15% of the preincision values. Additional doses of fentanyl (1.5 μg/kg IV) were administered to control acute hemodynamic responses that did not respond within 5 min to an increase in the inspired concentration of the volatile anesthetic.

During the maintenance period, vecuronium (0.01–0.03 mg/kg) was administered as necessary for muscle relaxation, which was monitored using a peripheral nerve stimulator. Ventilation was controlled to maintain normocarbia as measured by capnography. Anesthesia was maintained with a total gas flow of approximately 3.0 L/min, using a semiclosed circle system with carbon dioxide absorption by Baralyme (Allied Healthcare, St. Louis, Mo.). Body temperature was maintained at 36–37°C, using a forced air warming blanket (Bair Hugger, Augustine Medical, Eden Prarie, Minn.). Noninvasive blood pressure measurements, heart rate, hemoglobin oxygen saturation, esophageal temperature, and end-tidal CO_2 were recorded every minute from induction of anesthesia until 5 min after skin incision, and subsequently at 5-min intervals, using an integrated Cardiocap II monitor (Datex Medical Instrumentation, Tewksbury, Mass.). During the last 20–30 min of the procedure, the end-tidal concentration of the inhaled anesthetic was adjusted to 0.8–1.0 MAC concentrations. Morphine (0.05 mg/kg IV) was administered to all patients at this time to provide postoperative analgesia upon emergence from anesthesia. At the end of the procedure, residual neuromuscular blockade was reversed with neostigmine (40–80 μg/kg IV) and glycopyrrolate (8–16 μg/kg IV). Administration of the volatile anesthetic and nitrous oxide was discontinued simultaneously after reversal of neuromuscular blockade. The time of discontinuation of the anesthetic agent and the end-expired concentration at that time were recorded. Controlled ventilation with 8 L/min of oxygen was continued until the end-tidal nitrous oxide concentration was less than 10%.

The times at which the patients opened their eyes and responded to verbal commands were recorded. These emergence times were assessed at 15-s intervals after elimination of the anesthetic gases. Their tracheas were extubated when the patients were adequately recovered from the effects of neuromuscular blockade, had a regular breathing pattern, and were able to respond to the verbal command to squeeze the investigator's hand. The times at which the patients could state their name and date of birth were also recorded. Additional 1–2-mg intravenous bolus doses of morphine were administered in the early postoperative period if necessary to achieve adequate analgesia. Further blood samples to determine serum fluoride ion concentrations were obtained approximately 30 min after induction of anesthesia, immediately upon discontinuing the anesthetic, and at 1 h and 24 h after the end of anesthesia.

Data are expressed as mean values ± standard deviation (SD). Continuous variables were analyzed using analysis of variance (with Bonferroni multiple-comparison tests used to assess differences between the three groups). Changes in continuous variables over time were analyzed using paired *t*-tests. Descriptive (categorical) variables were analyzed using χ^2-tests. In all cases, P values <0.05 were considered to be statistically significant.

Table 1. Demographic Characteristics for the Three Anesthetic Treatment Groups[a]

	Group		
	I	II	III
Number of patients	25	25	25
Age (yr)	46 ± 12	44 ± 12	46 ± 11
Weight (kg)	72 ± 20	74 ± 18	75 ± 15
Race (black/white)	7/18	8/17	7/18
ASA physical status (I/II)	12/13	14/11	8/17
Procedures			
Abdominal hysterectomy	19	17	17
Vaginal hysterectomy	2	6	6
Laparotomy	4	2	2
Operating time (min)	134 ± 52	134 ± 58	137 ± 59
Anesthesia time (min)	153 ± 53	154 ± 59	157 ± 60
Blood loss (mL)	450 ± 325	425 ± 300	400 ± 300

Group I, propofol-isoflurane-nitrous oxide; group II, propofol-sevoflurane-nitrous oxide; group III, sevoflurane-nitrous oxide.

[a] Mean values ± SD (or numbers).

Table 2. Intravenous Fluid, Anesthetic, and Adjuvant Medication Requirements in the Three Anesthetic Treatment Groups[a]

	Group		
	I	II	III
Intravenous fluids (mL)	2775 ± 1225	2825 ± 1275	2675 ± 1075
Propofol (mg)	152 ± 38	147 ± 27	NA
Intraoperative fentanyl (μg/kg)	2.88 ± 0.86	2.82 ± 0.72	2.96 ± 0.60
Succinylcholine (mg)	109 ± 28	105 ± 18	107 ± 19
Vecuronium (mg)	5.1 ± 2.0	5.5 ± 2.9	5.3 ± 2.5
Intraoperative morphine (mg)	2.84 ± 2.1	2.94 ± 2.3	3.04 ± 2.4
Recovery room morphine (mg)	5.34 ± 4.6	4.52 ± 4.1	5.56 ± 3.8

Group I, propofol-isoflurane-nitrous oxide; group II, propofol-sevoflurane-nitrous oxide; group III, sevoflurane-nitrous oxide. NA, not applicable.

[a] Mean values ± SD.

Table 3. Induction of Anesthesia Characteristics for the Three Anesthetic Treatment Groups[a]

	Group		
	I	II	III
Induction time (s)	<60	<60	109 ± 25[b]
End-tidal concentration at loss of consciousness (%)	NA	NA	2.04 ± 0.62
Pain on injection	4% (1)	8% (2)	0
Cough	0	0	0
Apnea	4% (1)	0	0
Movement	4% (1)	0	0
Movement at intubation	24% (6)	24% (6)	36% (9)

Group I, propofol-isoflurane-nitrous oxide; group II, propofol-sevoflurane-nitrous oxide; group III, sevoflurane-nitrous oxide. NA, not applicable.

[a] Mean values (±SD) or percentage (number) of occurrences.

[b] Significantly different from control group (I), $P < 0.05$.

Results

The three groups were comparable with respect to age, weight, ASA physical status, race distribution, types and duration of surgical procedures, and blood loss (Table 1). In addition, patients received similar amounts of intravenous fluids, opioid analgesic, and muscle relaxants (Table 2). Analgesic requirements in the postanesthesia care unit (PACU) were also similar (Table 2).

The time to loss of consciousness in the patients receiving propofol (groups I and II) ranged from 30 to 85 s after the start of the injection. The time to loss of the eyelash reflex was significantly longer for inhaled induction of anesthesia with sevoflurane and nitrous oxide (109 ± 25 s). The end-tidal sevoflurane concentration recorded at loss of consciousness was 2.0% ± 0.6% (mean ± SD). Side effects and complications during induction of anesthesia are summarized in Table 3. A total of three patients (12%) receiving propofol complained of pain at the intravenous injection site. One patient in group I exhibited apnea and another demonstrated excitatory movements. Inhaled induction of anesthesia with sevoflurane was not associated with clinical signs of respiratory irritation, coughing, laryngospasm, or excessive oral secretions. As induction proceeded in group III, spontaneous ventilation became progressively more shallow, and manual assistance of ventilation was required immediately after loss of consciousness. A minor degree of movement after tracheal intubation was relatively common in all three groups (24%, 24%, and 36% in groups I, II, and III, respectively).

Changes in heart rate and mean arterial blood pressure (MAP) are shown in Figure 1. After induction of anesthesia, heart rate and mean arterial pressure decreased in all three groups. The decrease in MAP was significantly greater in the two groups (I and II) whose anesthesia was induced with propofol. After induction of anesthesia, MAP was 71 ± 11, 73 ± 12, and 80 ± 14 (P = 0.03) in groups I, II, and III, respectively. Laryngoscopy and tracheal intubation produced a transient increase in both heart rate and MAP, which was similar in all three groups and returned to preintubation values within 2 min. After skin incision, maintenance of heart rate and MAP within 15% of the preincision values was easily achieved in all three treatment groups by varying the inspired concentration of the volatile anesthetic. Although mean heart rate values were similar in all three groups, episodes of bradycardia (<50 beats/min) were more common in group II (5, 11, and 6 episodes in groups I, II, and III, respectively), two of which required treatment with anticholinergic medication because of associated hypotension (MAP < 65 mm Hg). In contrast, episodes of significant tachycardia (>110 beats/min) occurred equally in all three

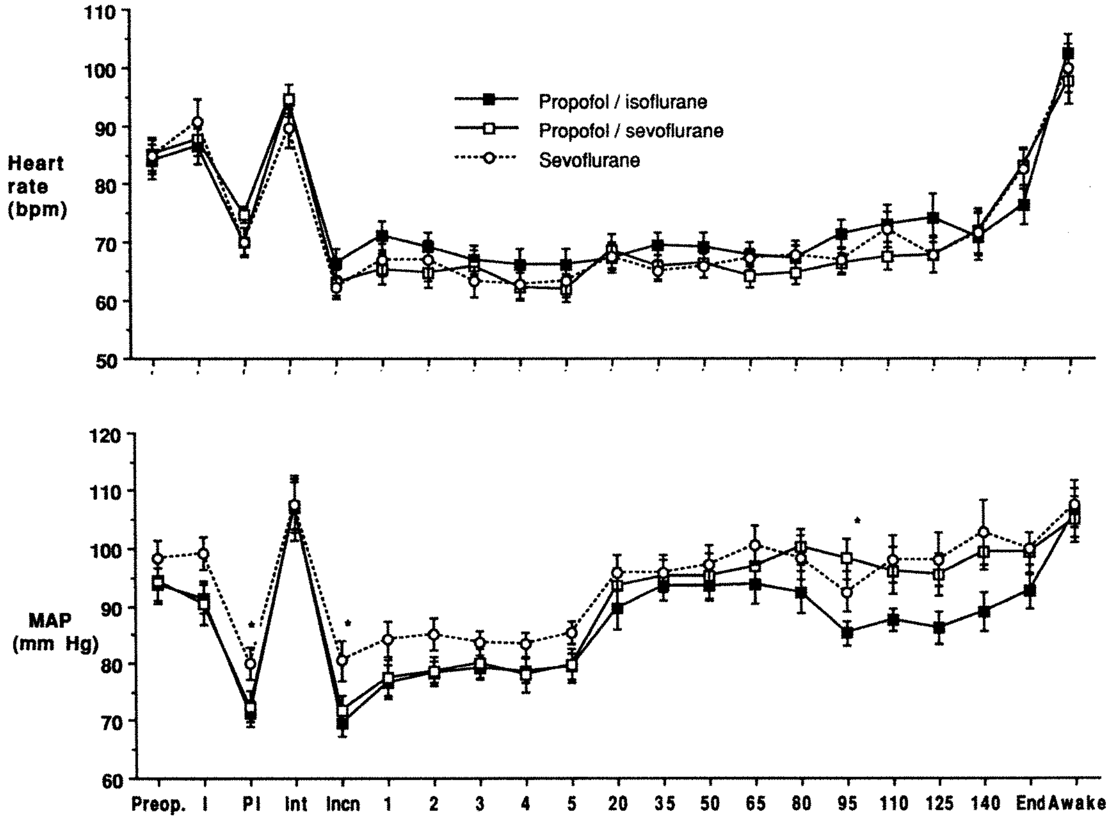

Figure 1. Changes in heart rate (*top*) and mean arterial blood pressure (*bottom*) from before induction of anesthesia (Preop.), at induction (I), after induction (PI), at intubation (Int), at skin incision (Incn), at the specified times in minutes from skin incision, at the end of anesthesia (End), and upon response to commands (Awake) in the three anesthetic treatment groups. Mean values ± SEM. $^*P < 0.05$, from control (group I).

groups (4, 4, and 3 episodes in groups I, II, and III, respectively).

During the maintenance period, the mean (±SD) end-tidal isoflurane concentration was 0.69% ± 0.17% (~1.2 MAC [3]) in group I and the average sevoflurane concentrations were 0.77% ± 0.28% (~1.2 MAC [4]) and 0.86% ± 0.35% (~1.3 MAC) in groups II and III, respectively. MAC values were calculated by taking the published MAC value for a middle-aged population and decreasing this value by 1% for every 1% of nitrous oxide used. Mean end-tidal nitrous oxide concentrations during the maintenance period were 62% ± 4%, 63% ± 3%, and 62% ± 3% in groups I, II, and III, respectively. At the end of anesthesia, the corresponding concentrations were 0.48% ± 0.13%, 0.55% ± 0.18%, and 0.64% ± 0.19% (or 0.86, 0.83, and 0.97 MAC) in groups I, II, and III, respectively.

Compared to the isoflurane group (I), the emergence times from cessation of the administration of the anesthetic agent to spontaneous eye opening, response to simple commands, extubation, and to correctly stating name and date of birth were significantly shorter in the sevoflurane groups (Figure 2). The morphine requirements, in the PACU, were 5.3 ± 4.6, 4.5 ± 4.1, and 5.6 ± 3.8 mg in groups I, II, and III, respectively. The requirement for opioid analgesic medication in the PACU precluded an objective assessment of later recovery events and effects of the anesthetics on recovery of cognitive function and psychomotor performance. There was no significant dif-

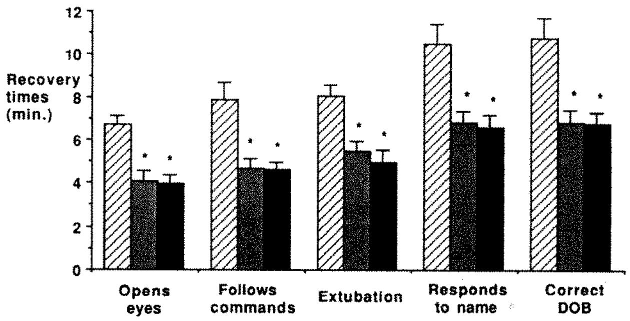

Figure 2. Times from discontinuation of the maintenance anesthetic agent until patients could open their eyes, follow commands, had tracheas extubated, and were able to give their names and correct date of birth (DOB). Bars are for group I, propofol/isoflurane (*hatched*), group II, propofol/sevoflurane (*light shaded*), and group III, sevoflurane alone (*solid*). Mean values ± SEM. $^*P < 0.05$, from control (group I).

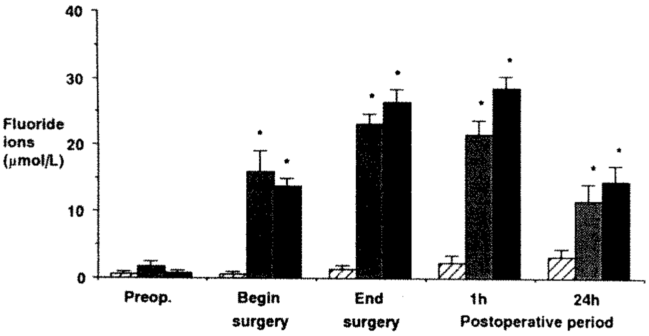

Figure 3. Levels of serum fluoride ions detected before induction of anesthesia (Preop.), 30 min after induction (Begin surgery), immediately after discontinuation of anesthesia (End surgery), 1 h postoperatively (1 h), and 24 h postoperatively (24 h). Bars are for group I, propofol/isoflurane (*hatched*), group II, propofol/sevoflurane (*light shaded*), and group III, sevoflurane alone (*solid*). Mean values ± SEM. *$P < 0.05$, from control (group I).

ference between the three groups with respect to the duration of stay in the PACU (114 ± 44, 123 ± 47, and 118 ± 37 min in groups I, II, and III, respectively).

Serum fluoride ion concentrations remained at or less than the limit of detection throughout the perioperative period in those patients receiving isoflurane. However, after exposure to sevoflurane for a period of 27 ± 7 min, fluoride levels were significantly higher than in those patients receiving isoflurane (Figure 3). The mean (± SD) fluoride levels at the end of the operation were 23.2 ± 7 and 26.4 ± 9 μmol/L in groups II and III, respectively. Serum fluoride values were similar 1 h after the end of anesthesia. Although still significantly higher than in the isoflurane group, fluoride levels 24 h postoperatively were significantly lower than the earlier postoperative values. Linear regression analysis revealed a correlation ($r^2 = 0.45$, $P < 0.05$) between the fluoride level detected at the end of the operation and the extent of exposure to sevoflurane as measured in MAC-hours (Figure 4). In contrast, there was no correlation between the fluoride level and the extent of exposure to isoflurane in the patients in group I (Figure 4). The highest fluoride level detected was 51.4 μmol/L in a patient (group III) having an operation lasting 327 min. Routine postoperative laboratory tests (e.g., electrolytes, blood urea nitrogen, creatinine, urine analysis) did not reveal evidence of fluoride-induced nephrotoxicity in any patient.

Discussion

Induction of anesthesia with sevoflurane was rapid and notable for the lack of respiratory irritation, despite the fact that high inspired concentrations (~5%) were administered from the outset. The speed of induction (109 ± 25 s) may have been limited by

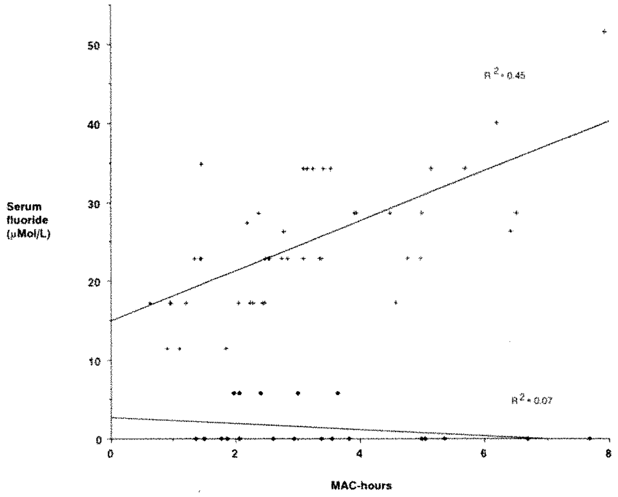

Figure 4. Correlation between serum fluoride ions measured immediately after the discontinuation of anesthesia and the anesthetic exposure in MAC-hours for the two groups receiving sevoflurane (groups II and III, *crosses*) and for the patients receiving isoflurane (group I, *solid symbols*).

the anesthetic output of the vaporizer (maximum setting of 5%). All patients received a small dose of fentanyl before induction of anesthesia to minimize the hemodynamic response to tracheal intubation (5). It is possible that inhaled induction with sevoflurane might have been less well-tolerated had an opioid analgesic not been administered before induction of anesthesia. During inhaled induction with sevoflurane, respiratory depression tended to develop with increasing end-tidal sevoflurane concentrations. Cardiovascular depression after induction of anesthesia with sevoflurane was significantly less than that seen after an induction dose of propofol (2 mg/kg IV). Propofol was used to induce anesthesia in groups I and II because its short elimination half-life would be less likely to interfere with the assessment of emergence and early recovery times than other commonly used intravenous induction agents (e.g., thiopental).

The expired concentration of sevoflurane recorded at the loss of the eyelash reflex was approximately 2%. However, this value does not necessarily correspond to the true alveolar concentration because the sample was obtained from a face mask that contained dead space. Movement in response to tracheal intubation was relatively common in all three groups and the hemodynamic response to laryngoscopy and tracheal intubation was not significantly different between patients receiving inhalation (sevoflurane) or intravenous (propofol) induction techniques.

Although MAP remained closer to preinduction baseline (awake) values during induction of anesthesia in patients receiving sevoflurane, intraoperative hemodynamics appeared similar in all three treatment groups. Bradycardia occurred more frequently in patients receiving sevoflurane after a propofol induction, whereas episodes of tachycardia occurred with equal frequency in all three groups. Although it has been suggested that sevoflurane produces a lower heart rate than does isoflurane, our data do not confirm this suggestion. However, the fact that two patients with bradycardias required treatment with an anticholinergic drug (because of the associated hypotension), and that hemodynamic values were used as the end points in anesthetic titration, might have obscured a difference between the two maintenance agents.

The end-tidal concentration of sevoflurane required to maintain a stable level of anesthesia, as indicated by clinical and hemodynamic signs, was similar to that for isoflurane (0.77 ± 0.28 and 0.86 ± 0.35 versus 0.69 ± 0.17 MAC, respectively). This is compatible with the previously reported sevoflurane MAC value of 1.71% (which is decreased to 0.66% with 63.5% nitrous oxide) in humans (4), only approximately 10% higher than the corresponding values for isoflurane (3).

Despite equipotent end-tidal concentrations at the end of anesthesia (0.86, 0.83, and 0.97 MAC, in groups I, II, and III, respectively) and similar intraoperative adjunctive medication (e.g., fentanyl, morphine, and muscle relaxants), patients in the sevoflurane groups (II and III) had significantly shorter emergence times than those receiving isoflurane. Emergence was equally rapid in groups II and III, suggesting that the use of propofol for induction of anesthesia had no effect on recovery after maintenance of anesthesia with sevoflurane. The administration of analgesic medication (morphine) at the end of the operation may have modified the emergence times in our patients; however, this effect would have been similar in all three treatment groups. We were unable to demonstrate a difference between the groups with respect to the duration of their PACU stay. After lower abdominal operations, a number of other factors (e.g., treatment of postoperative pain, nausea, vomiting, and hypovolemia) can influence the duration of the PACU stay.

The levels of inorganic fluoride ions increased rapidly after initiating administration of sevoflurane, as indicated by the high values detected within 30 min after induction of anesthesia. Fluoride levels measured after discontinuation of sevoflurane were comparable to those reported previously (6). These levels generally were less than the proposed threshold level associated with renal toxicity (7) and were similar to values reported after enflurane administration (8). Perhaps the low tissue solubility of sevoflurane will limit its potential for nephrotoxicity, because a larger proportion of the anesthetic would be excreted before undergoing metabolism (9). The levels of fluoride ions measured correlated with the extent of the patient's exposure to sevoflurane as measured in MAC-hours. It is interesting to note that the one value in excess of 50 μmol/L was recorded in the patient having the longest operation (327 min). In contrast, serum fluoride levels remained very low in patients receiving isoflurane, and these values were not correlated with the duration of exposure.

These data would suggest that careful evaluation of renal function is indicated when utilizing sevoflurane for prolonged surgical procedures (e.g., more than 3 h), or when high inspired concentrations of sevoflurane are used (e.g., when adjuvants such as opioids and nitrous oxide are not used). At low flow rates with a semiclosed system there is the potential for toxicity as a result of the products of the degradation of sevoflurane by soda lime (10). Although no clinical or laboratory signs of nephrotoxicity were seen in any of our study patients, our routine postoperative laboratory testing would not have detected subtle or transient changes in postoperative renal function.

This study can be criticized in that the investigators were not blinded as to the anesthetics because different techniques (intravenous versus inhalation) and vaporizers (Tec III versus Tec IV) were used. Although objective measures were used (e.g., automated recording of hemodynamic values), the possibility of observer bias cannot be completely excluded. The study could be further criticized in that the inspired concentrations of the inhaled anesthetics could be altered in response to hemodynamic variables and clinical signs of inadequate anesthesia (e.g., lacrimation, diaphoresis). Finally, as a result of the dead space of the face mask, it is difficult to relate end-expired measurements of anesthetic vapors to alveolar values (and hence to the MAC) during the induction phase.

Potential differences between the three treatment groups may have been partially masked by the use of other central-acting medications. In particular, the use of fentanyl, morphine, and nitrous oxide may have affected the recovery times. As we believed that these adjuvants were necessary to optimize the anesthetic conditions in this patient population, we standardized their use in all three groups. For similar reasons, lidocaine was administered as prophylaxis against the pain associated with propofol administration. As lidocaine can produce hemodynamic and central nervous system effects, an identical dose was administered to patients in all three treatment groups.

Our study was designed to mimic the clinical situation closely by allowing the anesthesiologist to titrate the inhaled anesthetic to maintain an adequate depth of anesthesia appropriate "for the comfort of the patient and the conduct of surgery" (11). In fact, after the initial stimulus of skin incision, hemodynamic variables, and hence inspired anesthetic concentrations, did not change significantly throughout the maintenance period in any of the treatment groups. We attempted to maintain a stable end-tidal concentration of the volatile agent (i.e., 0.8–1.0 MAC) for the last 20–30 min of the operation, so that emergence times could be assessed from equivalent steady-state concentrations of the maintenance drugs.

In conclusion, induction of anesthesia with sevoflurane is rapid and without significant side effects. Although bradycardia requiring treatment occurred in two sevoflurane-treated patients induced with propofol, maintenance with sevoflurane-nitrous oxide was associated with hemodynamic stability comparable to isoflurane. The use of sevoflurane resulted in faster emergence from anesthesia than after isoflurane; however, there were no differences in duration of PACU stay. The high serum fluoride levels associated with prolonged administration of sevoflurane suggest a potential for nephrotoxicity.

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Slow Injection Does Not Prevent Midazolam-Induced Ventilatory Depression

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To determine whether the risk of midazolam-induced ventilatory depression is related to the rate of midazolam administration, we compared the effect of rapid (over 15 s) and slow (over 5 min) administration of midazolam (0.1 mg/kg IV) on the hypercarbic ventilatory response of 10 healthy volunteers. During the first 5 min after the start of midazolam injection, the slope of the ventilatory response to CO_2 was significantly lower when the subjects received midazolam rapidly ($P < 0.001$). However, after completion of the infusion (between 5 and 20 min), depression of the CO_2 response curve slope was independent of the rate of midazolam administration. Similarly, although minute ventilation and tidal volume measured at an end-tidal CO_2 tension of approximately 46 mm Hg decreased more quickly after rapid administration of midazolam ($P < 0.001$), these variables did not differ significantly between the two rates of administration once the slow infusion was complete. These results suggest that slow administration of midazolam provides no independent protection from respiratory depression.

(Anesth Analg 1992;74:260–4)

Midazolam is commonly used to provide sedation for patients receiving regional anesthesia or monitored anesthesia care. When administered rapidly, however, midazolam may cause hypoventilation by virtue of its depressant effect on both the hypercarbic and hypoxic ventilatory drive mechanisms (1,2). It may also cause central and obstructive apnea (3) as well as decreases in tidal volume (4). Respiratory depression may be less likely to occur when midazolam is administered slowly (5); if this were true, patient safety could be enhanced by slowing the rate of midazolam administration. We conducted the present randomized, double-blind study to determine if the acute effect of midazolam on the ventilatory response to CO_2 is dependent on the rate of midazolam administration.

Methods

Ten male volunteers, 28–37 yr of age, consented to participate in this Institutional Review Board approved study. All were nonsmokers and had not used benzodiazepines for at least 14 days. Subjects refrained from alcohol or caffeine-containing beverages for 24 h and took nothing by mouth for 8 h before each of two study days. Upon their arrival in the laboratory, we weighed each subject, started an intravenous infusion of Normosol at a rate of 100 mL/h, and affixed arterial blood pressure and electrocardiographic monitors; we encouraged subjects to void before each ventilatory trial.

The supine subjects listened to symphonic music through occlusive headphones as they breathed mixtures of CO_2 and O_2 via a mask from the circuit shown in Figure 1; we kept the subjects' necks slightly extended to maintain airway patency. By varying the speed of the circulator, we adjusted the flow through the CO_2 absorber to keep end-tidal CO_2 tension ($P_{ET}CO_2$) constant (±1 mm Hg) despite changes in the subjects' ventilatory patterns. At a flow of 100 L/min, resistance to gas flow in the circuit was 0.02 cm $H_2O \cdot L^{-1} \cdot min$.

On each study day, subjects received 0.1 mg/kg of midazolam by one of two modes of intravenous injection—fast (over 15 s) or slow (by syringe pump over 5 min)—according to a randomization table. To maintain the double-blind nature of the study, subjects received a 0.9% sodium chloride placebo by the alternate mode of administration; neither the investi-

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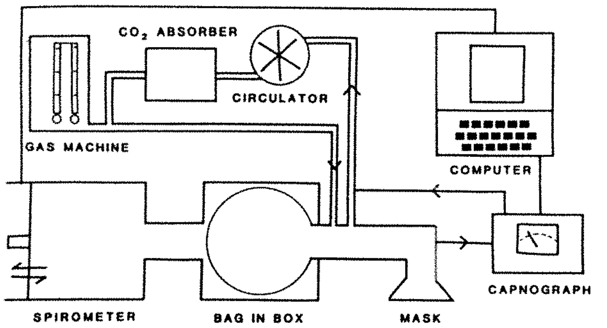

Figure 1. Breathing circuit with variable CO$_2$ absorption. We adjusted the speed of the circulator manually, based on breath-by-breath end-tidal CO$_2$ measurements, to keep $\mathrm{PETCO_2}$ constant ±1 mm Hg at either 46 or 58 mm Hg.

Table 1. Definition of Awareness Scores

4—Awake and alert
3—Awake but drowsy
2—Asleep but opens eyes to verbal command
1—Asleep, unresponsive to verbal stimulation, lash reflex present
0—Asleep, lash reflex absent

gators nor the subjects were aware of the syringe contents.

Before each trial, we maintained $\mathrm{PETCO_2}$ steady at approximately 46 or 58 mm Hg for alternate subjects (to eliminate any bias introduced by study sequence). After allowing 8 min for equilibration, we began the midazolam injection. For the next 20 min, we continuously recorded breath-by-breath values of minute ventilation, tidal volume, and $\mathrm{PETCO_2}$. At 1-min intervals, we verbally stimulated the subjects for approximately 5 s and noted the degree of responsiveness on a five-point scale (Table 1). After allowing subjects to recover for 4 h (with O$_2$ saturation monitoring), we retested each volunteer using the same mode of midazolam administration; by this time, blood concentrations of midazolam were expected to have declined to approximately 5% of their peak values (6), with normalization of the electroencephalographic spectrum. This time, however, we maintained the $\mathrm{PETCO_2}$ constant at 58 or 46 mm Hg, the value not studied in the earlier trial. Once again we recorded ventilatory variables for 20 min.

Three or more days after the first study session, each subject returned to complete the crossover phase of the study. This time, midazolam was administered either slowly (over 5 min) or rapidly (over 15 s), whichever mode was not used in the first study session. Again, we followed minute ventilation for 20 min at $\mathrm{PETCO_2}$ of 46 and 58 mm Hg.

An Instrumentation Laboratories End-tidIL 200 infrared CO$_2$ analyzer, calibrated with standard gas mixtures, continuously measured $\mathrm{PETCO_2}$. A dry spirometer (Electro/Med 780), calibrated with a 2-L calibrating syringe, measured ventilatory gas volumes, which we converted to BTPS using standard formulas. The CO$_2$ analyzer and spirometer were interfaced to a CBM 8032 computer by a multichannel analog-to-digital converter.

For each rate of midazolam administration, we determined the time-course of the CO$_2$ response curve as follows. At 30-s intervals after the start of midazolam administration, we determined five-breath averages of minute ventilation and $\mathrm{PETCO_2}$ at both low (≈46 mm Hg) and high (≈58 mm Hg) CO$_2$ tensions. In all cases, respiratory rates remained above 10 breaths/min; therefore, no breaths were counted twice. At any given time, the slope of the two-point CO$_2$ response curve is given by the difference in minute ventilation divided by the difference in the measured CO$_2$ tensions (≈12 mm Hg). Minute ventilation at $\mathrm{PETCO_2} \approx 46$ mm Hg ($\dot{V}\mathrm{E}46$) served as an index of displacement of the CO$_2$ response curve, and tidal volume at $\mathrm{PETCO_2} \approx 46$mm Hg (TV46) indicated changes in respiratory pattern.

We used two-way analysis of variance and the protected least-significant difference test (7) to compare the effects of the two rates of midazolam administration on the CO$_2$ response curve slope, $\dot{V}\mathrm{E}46$, and TV46 during two time periods: 0–5 min (i.e., after the rapid injection was complete but before the slow infusion was complete) and 5–20 min (i.e., after both the rapid and slow infusions were complete). We used paired *t*-tests to compare each subject's minimum slope, $\dot{V}\mathrm{E}46$, and TV46 after rapid injection with the corresponding minimum values after slow infusion. Kruskal-Wallis nonparametric analysis of variance compared awareness scores between the two rates of injection. Data are presented as mean ± SE, with $P < 0.05$ indicating significance.

Results

None of our subjects reported unpleasant sensations during or after midazolam injection. No subject lost consciousness or became apneic, or developed airway obstruction after midazolam. Arterial blood pressures remained within ±15% of baseline values, and heart rates remained within the normal range (50–100 beats/min). End-tidal CO$_2$ tensions were stable to within ±1 mm Hg during each hypercarbic drive determination. As might be expected, awareness scores were lower during the first 5 min after the start of rapid injection, during which time slow injection was not yet complete ($P < 0.001$, Figure 2).

Figure 3 displays the slope of the CO$_2$ ventilatory response curve as a function of time after the start of fast and slow administration of midazolam

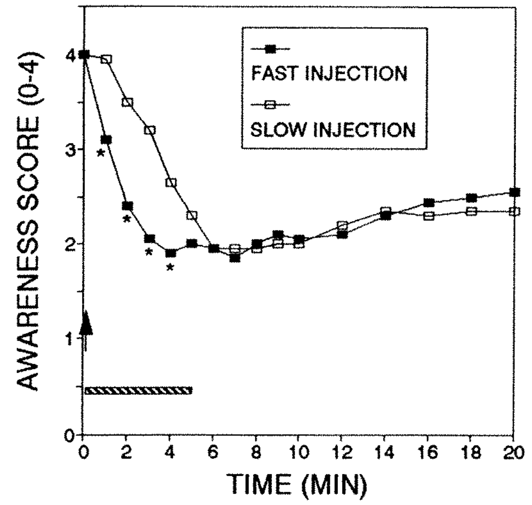

Figure 2. Comparison of awareness scores between rapid and slow rates of injection. The time of fast injection is indicated by the *arrow* and the duration of the slow injection is indicated by the *hatched line*. $^*P < 0.05$ between rates of injection at the indicated times.

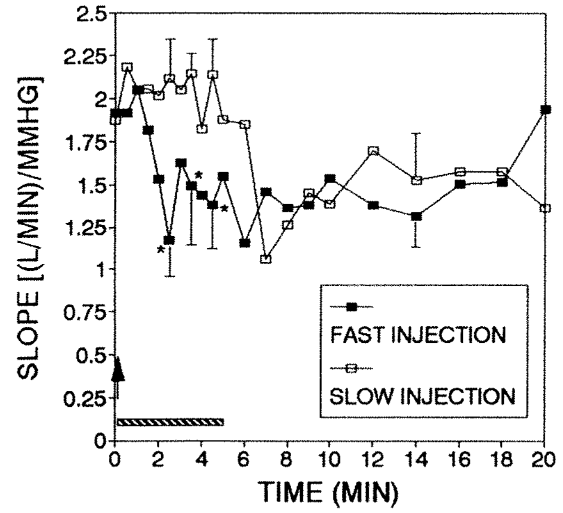

Figure 3. Comparison of the slope of the ventilatory response to CO_2 ($L \cdot min^{-1} \cdot mm\ Hg^{-1}$) between fast and slow rates of injection. The time of fast injection is indicated by the *arrow* and the duration of the slow injection is shown by the *hatched line*. Values are means with representative standard errors. $^*P < 0.05$ between rates of injection at the indicated times.

(0.1 mg/kg). During the first 5 min, slopes were significantly lower when subjects received midazolam by fast injection ($P < 0.001$). However, after completion of the infusion (5–20 min), the slopes did not differ between fast and slow administration, although both were decreased compared to their premidazolam values ($P < 0.001$). Minimum slope after rapid administration (0.38 ± 0.21 $L \cdot min^{-1} \cdot mm\ Hg^{-1}$) did not differ significantly from that observed after slow administration (0.50 ± 0.22 $L \cdot min^{-1} \cdot mm\ Hg^{-1}$).

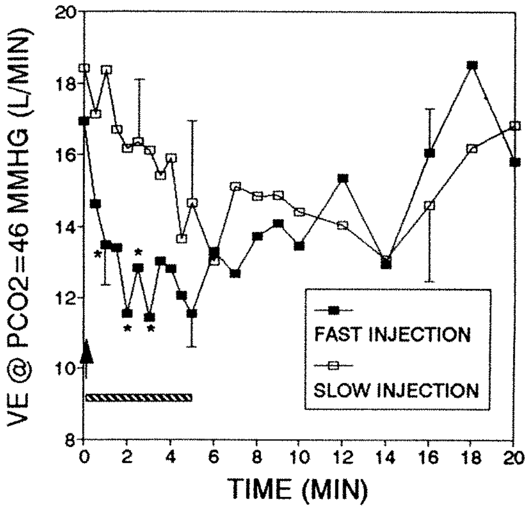

Figure 4. Comparison of minute ventilation (L/min) between fast and slow rates of injection. The time of fast injection is indicated by an *arrow* and the duration of slow injection is indicated by the *hatched line*. Values are means with representative standard errors shown. $^*P < 0.05$ between treatments at the indicated times.

The time-course of minute ventilation at $P_{ETCO_2} \approx$ 46 mm Hg ($\dot{V}_E46$) after injection of midazolam is displayed in Figure 4. Although this variable decreased more quickly after rapid administration of midazolam ($P < 0.001$ between groups during the first 5 min), the maximum downward displacement of the CO_2 response curve, as reflected by $\dot{V}_E46$, did not differ between the fast and slow modes of injection. The mean minimum value for $\dot{V}_E46$ after rapid administration (8.28 ± 0.76 L/min) did not differ significantly from that after slow administration (10.13 ± 1.57 L/min).

The effect of midazolam on $\dot{V}_E46$ was primarily the result of a decrease in tidal volume (Figure 5). During the first 5 min, tidal volumes were significantly lower when subjects received midazolam by fast injection than when they received it over 5 min ($P < 0.001$). Tidal volume did not differ between groups during the subsequent 15 min. Minimum tidal volume after rapid administration (0.44 ± 0.04 L) did not differ significantly from that after slow administration (0.54 ± 0.07 L).

Discussion

Midazolam is commonly used to provide sedation during regional anesthesia, monitored anesthesia care, endoscopic procedures, and outpatient oral surgery. Under these circumstances, respiratory depression may not be recognized, as patients who have received midazolam may not manifest autonomic signs of hypercarbia or hypoxemia such as hypertension, tachycardia, and restlessness (2).

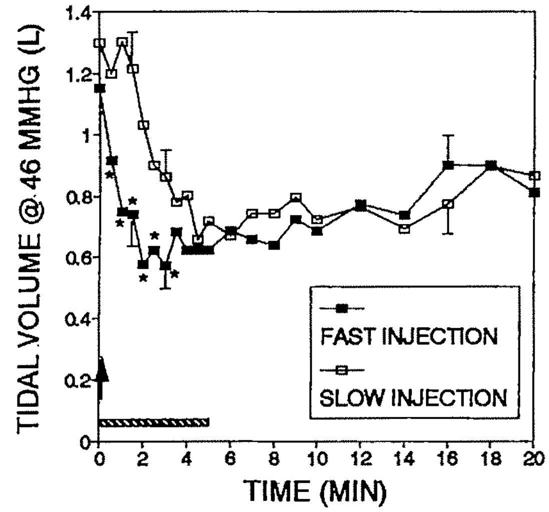

Figure 5. Comparison of the tidal volume (in liters at P_{ETCO_2} = 46 mm Hg) between fast and slow rates of injection. The time of fast injection is indicated by the *arrow* and the duration of the slow injection is shown by the *hatched line*. Values are means with representative standard errors shown. *$P < 0.05$ between treatments at the indicated times.

Therefore, unless oxygenation is monitored continuously, the first sign of respiratory insufficiency may be cardiac arrest. Indeed, cases of cardiorespiratory arrest have been reported in both the scientific and lay literature (8–10).

The manufacturer recommends that midazolam be not administered "by rapid or single bolus administration" (Package insert—midazolam. Hoffmann-LaRoche, Inc., Nutley, N.J.), on the unproven assumption that the lower peak blood levels associated with slower rates of drug administration are less likely to depress ventilatory drive. However, the present study shows that slow administration provides no independent protection from respiratory depression. During the first 5 min (when the rapid injection was complete, but infusion was ongoing), decreases in slope, displacement, and tidal volume were significantly greater when subjects received midazolam by fast injection; however, this difference disappeared after the slow injection was complete. Once subjects had received the same total dose of midazolam by slow injection as they had by fast injection (i.e., after 5 min), there was no difference in its effect on ventilatory control. Furthermore, the rate of midazolam administration did not significantly affect subjects' minimum CO_2 response slopes, or their minimum $\dot{V}_E$ or tidal volume at P_{ETCO_2} ≈ 46 mm Hg.

Midazolam has several distinct effects on ventilatory mechanics that contribute to alveolar hypoventilation. In agreement with previous findings (4), our data confirm the fact that midazolam's primary effect is to decrease tidal volume, causing a significant decrease in alveolar ventilation. At P_{ETCO_2} ≈ 46 mm Hg, our subjects' tidal volumes decreased by 50% after 0.1 mg/kg of midazolam, regardless of whether injection was made quickly (over 15 s) or slowly (over 5 min). This effect most likely results from a decrease in the central respiratory drive, as we positioned the subjects' heads to keep their airways open. It is likely that the decrease in tidal volume would be even more pronounced in those clinical situations where airway patency is not continuously maintained, as benzodiazepines may increase upper airway resistance by relaxing the genioglossus and associated musculature (11).

Central respiratory pauses frequently develop in patients after midazolam, during which pauses they may become hypoxemic (3). None of our subjects exhibited such pauses during the study as they were stimulated to breathe by elevated CO_2 tensions. Furthermore, despite the fact that they were breathing room air in the recovery room, none of the subjects became hypoxemic by pulse oximetry between 30 min and 4 h after midazolam was given. Interestingly, preliminary data suggest that slow administration of midazolam may not reduce the risk of hypoxemia in patients breathing room air (12).

The dual-isohypercapnic technique allows determination of ventilatory drive at frequent intervals after drug administration; however, it relies on the assumption that the effects of the first dose of midazolam have dissipated before the start of the second trial. Although we waited 4 h between trials (6), and despite the fact that subjects were fully awake, there may have been some residual ventilatory depression at the time of the second trial on each study day. By alternating the sequence of high versus low CO_2 trials, we minimized the likelihood that trial sequence caused a systematic error in our data. It was necessary to perform the two determinations for each rate of midazolam administration on the same day because of the day-to-day variability of ventilatory control. However, for each subject, the CO_2 sequence was the same for both rapid and slow midazolam administration, allowing for valid paired comparisons.

In conclusion, the magnitude of the effect of 0.1 mg/kg of midazolam on the slope and displacement of the ventilatory response to CO_2 did not depend on the rate of midazolam administration. Regardless of whether subjects received midazolam over 15 s or over 5 min, the degree of respiratory depression was the same; slow administration merely delayed the time when maximal depression occurred. Therefore, slow administration of midazolam, in and of itself, did not eliminate the risk of significant ventilatory depression. Rather, the present data suggest that midazolam should be administered in small, incremental doses; the decision to administer additional midazolam should be delayed for 2–3 min, until the respiratory depressant effects of previous doses have reached their peak.

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Sedation and Recovery of Psychomotor Function After Intravenous Administration of Various Doses of Midazolam and Diazepam

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A placebo-controlled, double-blind, crossover trial in 11 healthy male volunteers compared clinical sedation and psychomotor function after intravenous injection of midazolam (0.05, 0.1, or 0.15 mg/kg), diazepam (0.15 or 0.3 mg/kg), or placebo (saline). The depth of sedation was estimated at 5–10-min intervals during the first hour after injection. A comprehensive battery of psychomotor tests was used to collect objective data of psychomotor performance before drug injection and 1, 3, 5, and 7 h after injection. Midazolam (0.15 mg/kg) produced the highest scores of sedation and most impairment of psychomotor performance. In most tests, the maximal psychomotor effects seen after 0.3 mg/kg of diazepam did not reach those of 0.1 mg/kg of midazolam. Although the strongest psychomotor effects were induced by midazolam, these effects disappeared sooner than those of diazepam. By 5 h after injection, 0.3 mg/kg of diazepam showed the highest scores of psychomotor impairment. The authors conclude that at least four times as much diazepam as midazolam is needed to produce equally severe psychomotor impairment. That the residual effects of midazolam terminate sooner than those of diazepam probably accounts for the occasional underestimation of the potency of midazolam in clinical practice.

(Anesth Analg 1992;74:265–71)

Midazolam is a frequently used intravenous (IV) sedative with a short elimination half-life of approximately 2 h (1). However, during a 2-yr period, the Food and Drug Administration received 57 reports of severe cardiovascular or respiratory complications involving 30 deaths and four cases of hypoxic encephalopathy (FDA: personal communication, 1988). Although the potency of midazolam is about two times that of diazepam (2), recent evidence indicates that this ratio is too low (3) and that much smaller doses of midazolam should be used. Therefore, our study investigated the clinical sedation and psychomotor performance of healthy male volunteers after IV administration of placebo and various doses of diazepam and midazolam.

Methods

This study was approved by The University of Chicago Clinical Investigation Committee, and written consent was obtained from each participant. Eleven healthy male volunteers (23.1 ± 4.7 yr, 68.7 ± 10.2 kg, 174.0 ± 7.2 cm; mean ± SD) participated in the study. None were receiving medications, and none had a history of mental or neurologic illness. All were social drinkers who used alcohol moderately one to six times a month. Participants were instructed to abstain from any medication and drugs (including marijuana) during the entire trial and from alcohol for 3 days before tests. Subjects fasted from midnight the night before testing until the time of testing; all received a light standard meal 5.5 h after drug injection.

This double-blind, randomized, placebo-controlled, crossover trial studied the effects of different doses of intravenously administered midazolam or diazepam on psychomotor skills in six successive test sessions, allowing a 1-wk washout interval between treatments. Before entering the study, all subjects practiced using the test apparatus on several occa-

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sions to minimize the possibility of learning the tasks during the study period.

Each test morning the subjects received a slow IV injection of saline, one of three doses of midazolam (0.05, 0.1, or 0.15 mg/kg), or one of two doses of diazepam (0.15 or 0.3 mg/kg). Depth of sedation was estimated at 5, 10, 15, 20, 30, 40, and 50 min after injection. Psychomotor function was evaluated 1 h before injection (baseline), and the test battery was repeated 1, 3, 5, and 7 h after injection. The individual tests were always repeated in the same order, and the completion of the test battery took 30 min.

Inability to remember a painful stimulus (hereafter referred to as "amnesia") was assessed similarly to Korttila and Linnoila (4): The subject's abdomen was pinched 5 min after injection, and 2 h later, the subject was asked if he remembered being pinched at 5 min.

Magnitude of sedation was estimated according to the following scale: 1 = subject awake (resting with eyes open); 2 = subject asleep and easily aroused (opens eyes and responds after name is called twice in a normal voice); 3 = subject asleep and difficult to arouse (responds only after name is called loudly or shaken by the shoulders); and 4 = subject asleep and unarousable (does not respond to a loud voice and shaking).

The computer-assisted psychomotor tests we developed use a Macintosh computer and the following definitions (5). *Auditory* and *visual reaction times* were the mean times necessary for subjects to press the computer keyboard space bar in response to 10 successive visual stimuli and later to 10 auditory stimuli. To establish *multiple reaction time*, subjects were to press specific keys of the keyboard only after the occurrence of a particular visual stimuli (the appearance of specific letters on specific sides of the computer screen), auditory stimuli (the presence or absence of a tone), or a combination of both visual and auditory stimuli. On each test occasion, a total of 40 stimuli were presented. *Divided-attention mistakes* and *correct responses* were measured by presenting the subjects with increasingly higher numbers, delivered simultaneously at the rate of one number every 1–1.5 s in each of the four quadrants of the computer screen. When the number "9" appeared, subjects had to note the quadrant and press the corresponding letter on the computer keyboard. *Coordination accuracy* and *mistakes* were measured by tracking a randomly moving target on the computer screen for 120 s using a Macintosh "mouse." "Accuracy" was the average distance (measured in pixels) between the center of the target and the location of the mouse. "Mistakes" referred to the number of times the distance between the mouse and target exceeded 1 cm.

Psychomotor tests of other type were also included in the test battery. *Body sway* was measured with a strain-gauge platform (Kistler Instrumente AG, Winterthur, Switzerland) connected to the computer. Subjects stood on the platform for 30 s with their eyes closed. The movement of the center point of gravity of their body was registered by the platform and graphed. The total graph lengths thus obtained, reflecting the amount of body sway, were measured. The amount of *exophoria* (deviation of the visual axis of one eye away from that of the other), expressed as the power of the prism (in diopters) used to prevent deviation, was measured with the Maddox wing device (6). Attention and coordination were evaluated by an *action judgment* tester (5). In this test, the subject uses a steering wheel to keep two pointers properly positioned on a moving track. The *digit-symbol substitution* test measured changes in sensory processing performance and the ability to concentrate (7). Subjects had to pair digits to symbols correctly for 2 min. Finally, using 100-mm-long visual analogue scales, participants subjectively estimated impairment of their *overall performance*, mental acuity (assessed as *mental slowness*), physical coordination (assessed as *clumsiness*), and body stability (assessed as *dizziness*). Estimates could range from "none" to "extreme."

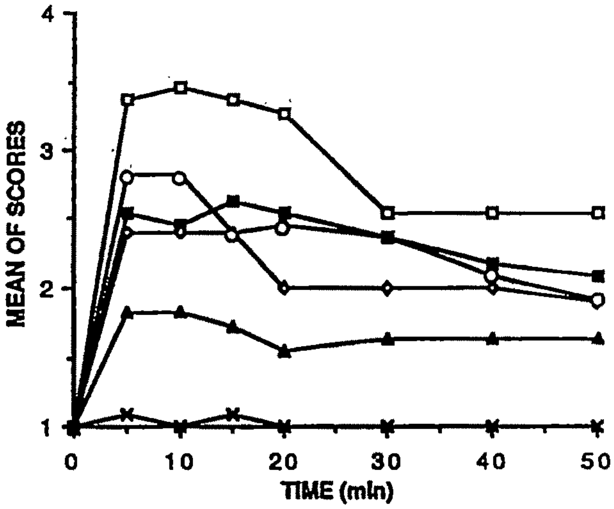

Figure 1. Mean score of sedation after IV injection of midazolam (◇, 0.05 mg/kg; ○, 0.1 mg/kg; □, 0.15 mg/kg), diazepam (▲, 0.15 mg/kg; ■, 0.3 mg/kg), and placebo (x, saline) in 11 volunteers.

A P value <0.05 was considered statistically significant. For each psychomotor test, a two-way analysis of variance (ANOVA) first determined significant differences between any of the treatments (interaction of time and treatment). Then, at each test time, one-way ANOVA (for repeated measures) was applied to detect differences between the six treatments. If results were significant, the Fisher's protected least significant difference test was used as a post hoc test

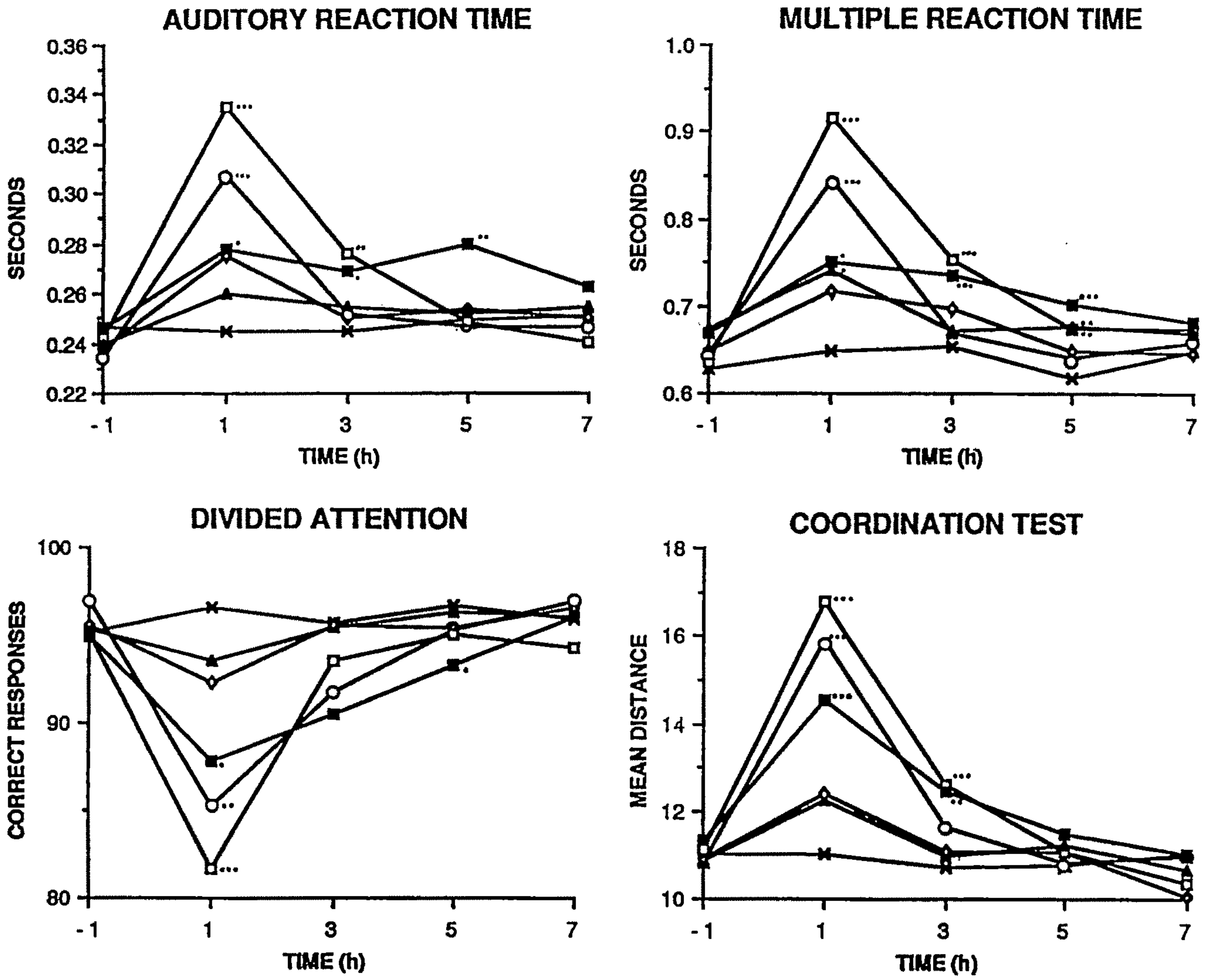

Figure 2. Auditory reaction time, multiple reaction time, correct responses in divided attention test, and coordination accuracy. Mean scores obtained before and after IV injection of midazolam (◇, 0.05 mg/kg; ○, 0.1 mg/kg; □, 0.15 mg/kg), diazepam (▲, 0.15 mg/kg; ■, 0.3 mg/kg), and placebo (x, saline) in 11 healthy volunteers. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs placebo; Fisher's protected least significant difference test.

to assess whether differences between individual pairs of treatments were significant. Amnesia and sedation were compared with Fisher's exact probability test.

Results

All subjects given 0.3 mg/kg of diazepam or 0.1–0.15 mg/kg of midazolam had complete amnesia because they could not remember if their abdomen was pinched. Seven subjects given 0.15 mg/kg of diazepam ($P < 0.05$ vs 0.3 mg/kg of diazepam and 0.15 mg/kg of midazolam) and nine given 0.05 mg/kg of midazolam could not remember being pinched. With placebo there was no amnesia.

Figure 1 shows the mean scores for clinical sedation. The sedative effects of midazolam and diazepam were dose-dependent. The maximum effect obtained with 0.3 mg/kg of diazepam was between the maximum effects of 0.05 and 0.1 mg/kg of midazolam suggesting a dose ratio of 4–5:1 for equipotent doses for sedation. Six subjects were unarousable 5 min after injection of 0.15 mg/kg of midazolam and three subjects after the dose of 0.10 mg/kg, whereas all subjects were arousable after 0.05 mg/kg of midazolam or 0.30 or 0.15 mg/kg of diazepam (midazolam: 0.15 vs 0.10 mg/kg, $P < 0.05$; midazolam: 0.15 vs 0.05 mg/kg or vs 0.15 or 0.30 mg/kg of diazepam, $P < 0.01$; midazolam: 0.10 vs 0.05 mg/kg or vs 0.15 or 0.30 mg/kg of diazepam, $P < 0.05$).

For all psychomotor tests, two-way ANOVA showed that overall differences between various drug

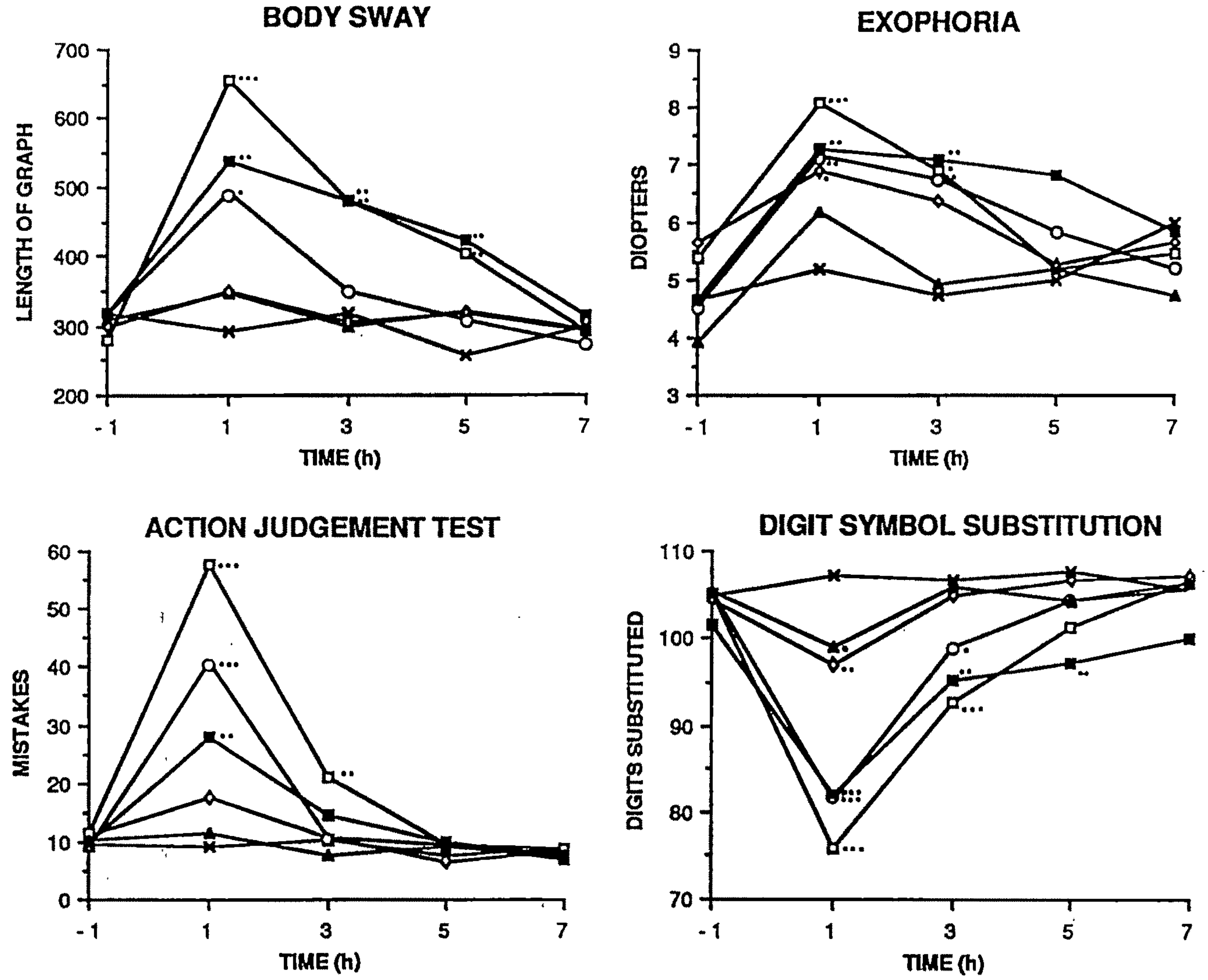

Figure 3. Body sway, exophoria, action judgment test mistakes, and digits correctly substituted. Mean scores obtained before and after IV injection of midazolam (◇, 0.05 mg/kg; ○, 0.1 mg/kg; □, 0.15 mg/kg), diazepam (▲, 0.15 mg/kg; ■, 0.3 mg/kg), and placebo (x, saline) in 11 healthy volunteers. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs placebo; Fisher's protected least significant difference test.

treatments were significant ($P < 0.05$ to 0.001). In addition, for all tests, one-way ANOVA revealed no significant differences between test days regarding baseline performance. On the other hand, at each test time after injections, one-way ANOVA revealed several significant differences between various treatments. The results of pairwise comparisons between various treatments for the psychomotor tests presented in Figures 2–4 are shown in Table 1.

All doses of midazolam impaired performance, as measured both objectively using tests of psychomotor function and subjectively using visual analogue scales. However, compared with placebo, the 0.05-mg/kg dose produced a significant difference only in the digit-symbol substitution test, the number of coordination mistakes, exophoria, and subjective estimation of overall performance. The 0.1- and 0.15-mg/kg doses produced significant differences in all objective and subjective tests 1 h after injection. With the 0.1-mg/kg dose, the only tests remaining significantly different from control for 3 h were the digit-symbol substitution test and the amount of exophoria. However, at 3 h, the effects of the 0.1-mg/kg dose of midazolam did not differ from the effects of placebo for other tests. With the 0.15-mg/kg dose of midazolam, psychomotor impairment remained significantly different for 3 h except for the divided-attention test. Five hours after injection, multiple reaction time and anterior-posterior body sway were still significantly impaired, whereas performance in the other tests was close to that produced by placebo.

Generally, the maximal effects after diazepam were not as prominent as those seen after midazolam. However, the psychomotor effects of diazepam lasted

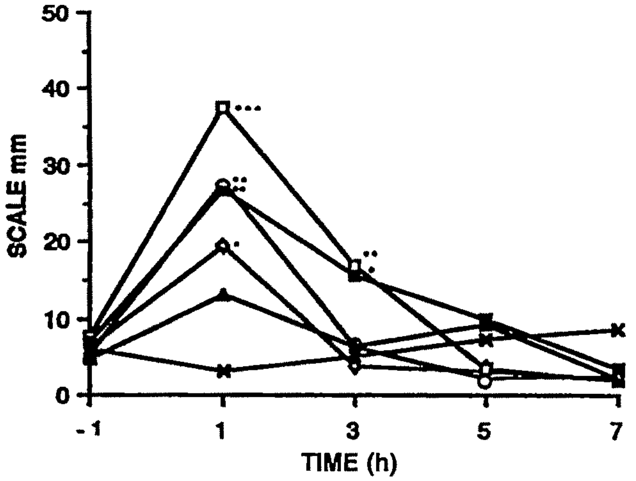

Figure 4. The participants' subjective estimate of worsened overall performance before and after IV injection of midazolam (◇, 0.05 mg/kg; ○, 0.1 mg/kg; □, 0.15 mg/kg), diazepam (▲, 0.15 mg/kg; ■, 0.3 mg/kg), and placebo (x, saline) in 11 healthy volunteers. *$P < 0.05$, **$P < 0.01$, *$P < 0.001$ vs placebo; Fisher's protected least significant difference test.

longer. One hour after injection, the 0.15-mg/kg dose of diazepam induced significant impairment only in the digit-symbol substitution test and in multiple reaction time. The 0.3-mg/kg dose significantly impaired performance in all tests. In seven tests, the performance remained impaired for 5 h after injection. Usually at this time the effects of midazolam were no longer detectable.

For the reaction tests, coordination test, and action judgment test, the highest scores seen after the 0.15-mg/kg dose of midazolam were statistically significantly greater than the highest scores seen after the 0.3-mg/kg dose of diazepam. The highest scores seen after the 0.3-mg/kg dose of diazepam did not usually reach the effects of the 0.1-mg/kg dose of midazolam. Hence, the dose-response relationship for the maximal psychomotor effects suggests that three to six times larger doses of diazepam must be used to obtain similar effects to those measured after midazolam.

Discussion

According to results from our laboratory measuring the psychomotor effects of alcohol (5), the new computerized test battery also proved sensitive to the effects of benzodiazepines. Baseline values always remained at the same level throughout the 6-wk experiment, and scores obtained after placebo remained at a constant level. Therefore, pretraining to avoid learning during actual testing was adequate, and the deviations found after drug injection were real treatment-related effects.

Intravenous diazepam and midazolam produced dose-related amnesia and sedation, impaired objective performance, and induced subjective effects characteristic of sedative drugs. With the doses tested, the most profound impairment in psychomotor function was seen at 1 h after injection of 0.15 mg/kg of midazolam. Recovery of psychomotor performance was faster after midazolam than after diazepam; statistically significant impairment (reaction times, divided attention, body sway, digit-symbol substitution) after 0.3 mg/kg of diazepam was still detectable 5 h after injection.

Dundee et al. (2) suggested that the estimated ratio of equipotent doses of diazepam and midazolam is approximately 2:1 and that the difference between the clinical effects of midazolam and diazepam is not very prominent when this dose ratio is used. In one study, comparing a mean dose of midazolam of 0.14 mg/kg with a 0.29-mg/kg dose of diazepam, the sedation was comparable (8). Though IV midazolam was faster than IV diazepam both in achieving sedation and in return to normal activities in outpatients, objective differences in psychomotor testing were not found in that study. In another study of ambulatory patients undergoing bronchoscopy with local anesthesia and either 0.2 mg/kg IV of diazepam or 0.05 or 0.1 mg/kg of IV midazolam for sedation, psychomotor performance was similar between patients and, 2 h after administration, similar to that before sedation (9). In a further study, the degree of sedation during recovery, discharge times, and postoperative Trieger test scores were similar for patients given 0.1–0.3 mg/kg of diazepam and those given 0.05–0.15 mg/kg of midazolam (10). Other psychomotor recovery tests also suggest that full recovery after midazolam takes about the same time as after diazepam (11).

Few studies used volunteers and various doses to carefully compare recovery from IV midazolam with recovery from IV diazepam. In one such study, volunteers given either 5 mg of midazolam or 10 mg of diazepam intravenously were tested for various psychomotor skills, including letter deletion, visual reaction time, addition, and seven-digit recall (3). Results showed that midazolam was more than twice as potent as diazepam. After 3 h, the impairment of psychomotor skills showed signs of reversal, with subjects receiving midazolam beginning to improve more rapidly than those receiving diazepam.

Immediate recovery (awakening) after a single IV injection of a sedative dose depends largely on the drug's distribution half-life (12). Recovery occurs when the central nervous system concentration declines below threshold level because of the redistribution of the drug to inert tissues (fat, muscle, skin). This explains why recovery after diazepam is relatively fast when compared with its long elimination

Table 1. Statistical Pairwise Comparisons of Midazolam (0.05 mg/kg [M 0.05], 0.1 mg/kg [M 0.10], and 0.15 mg/kg [M 0.15]) and diazepam (0.15 mg/kg [D 0.15] and 0.3 mg/kg [D 0.30])

Test	Time (h)	M 0.5 versus				M 0.10 versus			M 0.15 versus		D 0.15 versus
		M 0.10	M 0.15	D 0.15	D 0.30	M 0.15	D 0.15	D 0.30	D 0.15	D 0.30	D 0.30
Auditory reactions	1	*a*	*c*				*b*		*c*	*c*	
	3		*a*			*a*			*a*		
	5				*a*			*b*		*b*	*b*
Multiple reactions	1	*b*	*c*				*a*	*a*	*c*	*a*	
	3		*a*			*c*		*c*	*c*		*b*
	5				*b*			*b*			
Divided attention	1	*a*	*b*				*a*		*b*		
	3										
	5				*a*			*a*		*a*	*c*
Coordination	1	*c*	*c*		*a*		*c*		*c*	*a*	*b*
	3		*b*		*a*				*b*		*b*
	5										
Body sway	1		*c*		*a*	*a*			*c*		*a*
	3		*b*		*b*	*a*		*a*	*c*		*c*
	5							*a*			
Exophoria	1								*a*		
	3						*a*		*a*		*a*
	5										
Action judgment	1	*b*	*c*				*c*		*c*	*c*	*a*
	3		*b*			*b*			*c*	*a*	*a*
	5										
Digit-symbol substitution	1	*c*	*c*		*c*		*c*		*c*		*c*
	3		*c*		*b*		*a*		*c*		*b*
	5				*b*			*a*			*a*
Subjective performance	1		*a*						*c*		
	3		*b*		*b*				*a*		*a*
	5										

M, midazolam; D, diazepam.
Data refer to psychomotor tests presented in Figures 2–4 and time points 1, 3, and 5 h after injection.
$^aP < 0.05$, $^bP < 0.01$, $^cP < 0.001$; Fisher's protected least significant difference test.

half-life. After the drug redistribution, the residual psychomotor effects are more dependent on drug elimination and adaptation or acute tolerance (13,14). Intravenously administered diazepam has a distribution half-life of close to 1 h and a half-life of elimination of more than 30 h (15); in contrast, midazolam has an initial distribution half-life of 7.2 min and an elimination half-life of 2.5 h (16). Furthermore, because of midazolam's much shorter elimination half-life than the parent drug (17), the main active metabolite of midazolam, α-hydroxymidazolam, is probably not responsible for the prolonged effects reported earlier. The major metabolite of diazepam, desmethyldiazepam, has properties similar to its parent drug and has a much longer elimination half-life than diazepam. The pharmacokinetic profiles of midazolam and diazepam do not support the assumption of previous clinical studies suggesting that residual psychomotor effects after midazolam are similar to diazepam if equipotent doses are used.

Depending on the dose range studied and the tests measured, our results clearly indicate that the ratio of doses necessary to produce similar sedation and psychomotor peak effects of diazepam and midazolam is 3–6:1 rather than 2:1 as suggested earlier. Thus, clinically sufficient sedation may be achieved with smaller doses of midazolam than was recommended in the past. The earlier errors in estimation of the potency of midazolam may have been a result of the fact that the effects of a more potent dose of midazolam may be equivalent to the effects of a less potent dose of diazepam if the estimation is made 2–3 hours after drug administration.

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Anesthetic Drugs and Emergency Departments

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Hospital emergency departments were surveyed on their use of N_2O, intravenous anesthetics, and neuromuscular blocking drugs; patient monitoring during their use; and the monitoring and evaluation of the quality and appropriateness of the use of these drugs. We received 90 of the 170 surveys sent for a response rate of 53%. Sixty-three percent of the emergency departments that answered our survey administer one or more of these drugs in the emergency room. Less than two-thirds of these respondents indicated they use patient monitors while administering these drugs. The emergency department monitors and evaluates the appropriate use of these drugs in about half of the hospitals that use them, whereas the anesthesiology department is involved less than 20% of the time. Anesthesiology departments should become more involved in developing criteria for evaluating the quality of anesthesia administered by other hospital departments to help ensure that all patients receive a comparable level of anesthetic care throughout the hospital.

(Anesth Analg 1992;74:272–5)

Drugs commonly administered by anesthesiologists in the operating room are being used in many other areas of the hospital by nonanesthesiologists. One area in which anesthetic drugs are thought to be frequently used is the Emergency Department (ED). The extent to which ED physicians use anesthetic drugs, how patients are monitored, and if the hospital's anesthesia service is involved in maintaining the standard of care are not known. This study investigated the use of intravenous anesthetics, nitrous oxide, and neuromuscular blocking drugs; how patients were monitored; and who was responsible for monitoring and evaluating the quality and appropriateness of anesthetic care in the ED.

Methods

Survey forms were sent to the ED directors in hospitals with a capacity of 300 beds or more in the states of Illinois and Wisconsin. The survey specifically asked if N_2O, intravenous ultrashort-acting anesthetics (e.g., thiopental), and neuromuscular blocking drugs were used by ED physicians. If any of these drugs were used, survey respondents were asked (a) who was responsible for ensuring that the drugs were used in the appropriate situation and proper dosage and (b) to describe patient monitoring. Differences in responses between states were evaluated using χ^2-square tests.

Results

We received 90 of the 170 surveys sent, for a response rate of 53%. There were no significant differences between the two states in responses to any of the questions on the survey.

Of the EDs that responded to our survey, 30% (n = 27) administered N_2O (Figure 1), 20% (n = 18) administered intravenous ultrashort-acting anesthetics (Figure 2), and 53% (n = 48) administered neuromuscular blocking drugs (Figure 3). Where these drugs were used, evaluation of the quality and appropriateness of their use was performed by the ED in 48% (n = 13), 44% (n = 8), and 52% (n = 25) of the hospitals for N_2O, intravenous anesthetics, and neuromuscular blocking drugs, respectively. The anesthesiology department evaluated the quality and appropriateness of the use of N_2O, intravenous anesthetics and neuromuscular blocking drugs in 19% (Figure 1), 6% (Figure 2), and 4% (Figure 3), respectively, of the EDs that used them. In total, 63% (n = 57) of the EDs administered N_2O, intravenous anesthetic drugs, and/or neuromuscular blocking drugs (Figure 4). In 58% (n = 33) of these EDs, patients who received any of these drugs were monitored with one or more monitors including electrocardiogram, pulse oximetry, and arterial blood pressure (Figure 4). A single monitor was used by 24% (n = 8) of these EDs, two

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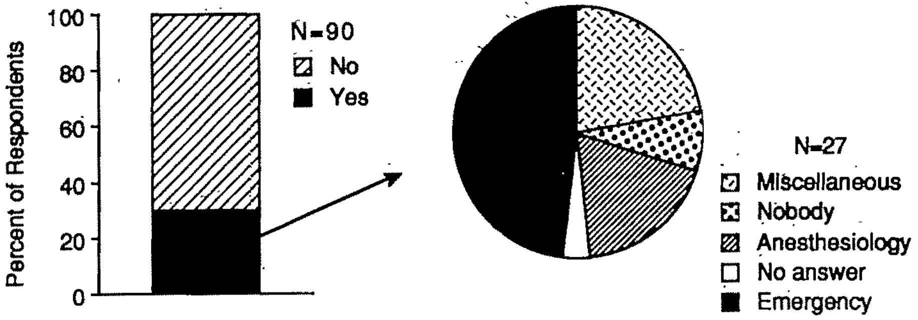

Figure 1. Thirty percent of emergency departments (ED) that answered our survey administer N_2O in the emergency room (*left*). The quality and appropriateness of the use of N_2O is monitored and evaluated by the ED (48%), the anesthesiology department (19%), other departments in the hospital (22%), or is not monitored at all (7%) (*right*). Four percent of respondents that use N_2O in the ED did not indicate who monitored and evaluated the quality and appropriate use of this drug.

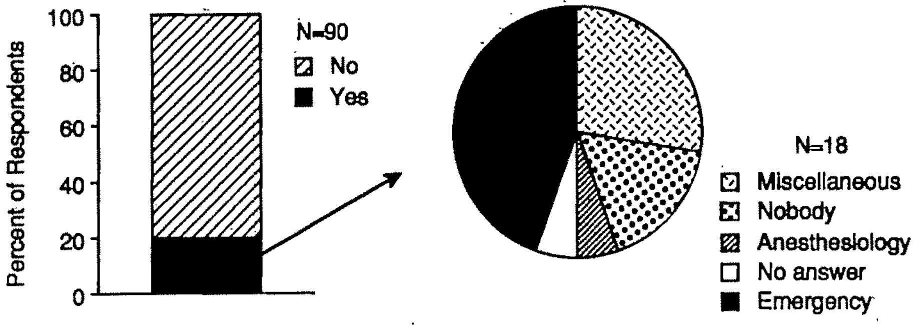

Figure 2. Twenty percent of emergency departments (ED) that answered our survey administer intravenous ultrashort-acting anesthetics in the emergency room (*left*). The quality and appropriateness of the use of intravenous ultrashort-acting anesthetics is monitored and evaluated by the ED (44%), the anesthesiology department (6%), other departments in the hospital (28%), or is not monitored at all (17%) (*right*). Five percent of the EDs that use intravenous ultrashort-acting anesthetics did not indicate who monitored and evaluated the quality and appropriate use of these drugs.

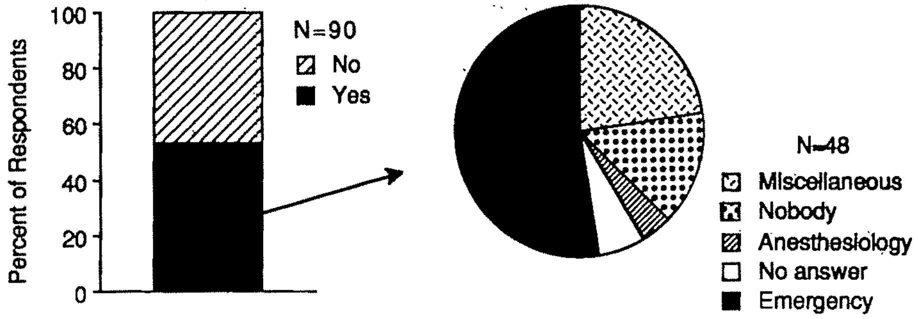

Figure 3. Fifty-three percent of emergency departments (ED) that answered our survey administer neuromuscular blocking drugs in the emergency room (*left*). The quality and appropriateness of the use of paralytic doses of muscle relaxants is monitored and evaluated by the ED (52%), the anesthesiology department (4%), other departments in the hospital (23%), or is not monitored at all (15%) (*right*). Six percent of the EDs that use neuromuscular blocking drugs did not indicate who monitored and evaluated the quality and appropriate use of these drugs.

monitors by 33% (n = 11), three monitors by 39% (n = 13), and four monitors by 3% (n = 1). No monitors were used in 12% of EDs administering these drugs, and 30% of the respondents that used these agents did not indicate whether or not they used monitors.

Discussion

One of the major goals of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) is to help set standards to assure the quality, safety, and appropriateness of patient care services. Inherent

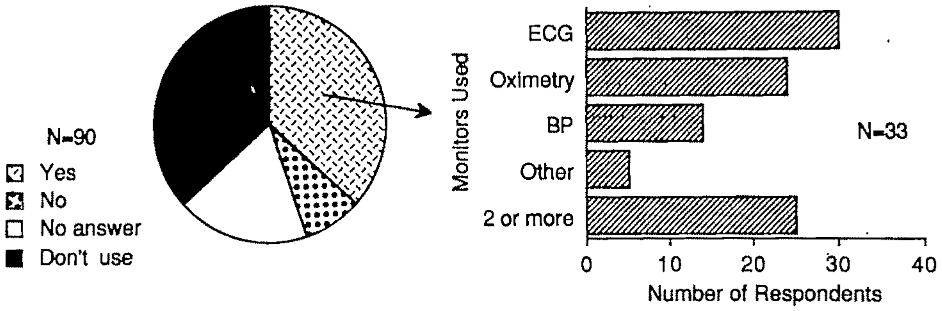

Figure 4. Thirty-seven percent of emergency departments (ED) that answered our survey use monitors while administering N_2O, intravenous induction agents, and/or neuromuscular blocking agents in the emergency room (*left*), 8% do not use monitors while administering these drugs, and 19% of the EDs responded that they use these drugs but did not indicate whether or not monitors were used. The remaining 37% do not use these drugs in their EDs. Monitors were used by 33 (58%) of the 57 EDs that administer one or more of these drugs, including (*right*) electrocardiogram ($n = 30$), pulse oximetry ($n = 24$), blood pressure ($n = 14$), and/or other monitors ($n = 5$). Twenty-five survey respondents indicated they use two or more monitors while administering these agents.

to providing appropriate quality of care for patients is the need to monitor and evaluate these services.

In the JCAHO Accreditation Manual for Hospitals (1) under the Surgical and Anesthesia Services section, the anesthesia standards apply "to all patients who receive general, spinal, or other major regional anesthesia or undergo surgery or other major regional anesthesia and/or intravenous, intramuscular, or inhalation sedation/analgesia that, in the manner used in the hospital, may result in the loss of the patient's protective reflexes." Furthermore, in the same section, criteria for individuals administering these services are stated: "Individuals who provide surgical and anesthesia services independently have appropriate clinical privileges to do so" and that "individuals who provided surgical or anesthesia services under direction or supervision have been determined to be competent to provide such services" (1).

By JCAHO standards, the anesthesia service, or specifically the director of anesthesia services, is responsible for developing "approaches to effectively monitor and evaluate the quality and appropriateness of anesthesia care provided by individuals in any department/service in the hospital including, but not necessarily limited to, the ambulatory care, dental, emergency, obstetric, psychiatric, special care, and special procedure(s) units/departments/services" (1). The goal of these standards is to ensure that patients with similar health problems and conditions receive a comparable level of anesthetic care throughout the hospital. The American Society of Anesthesiologists (ASA) also supports these standards. In the ASA 1991 Directory of Members (2) in the Medico-Administrative Organization and Responsibilities section, the responsibility of the director of the anesthesia department is to monitor the quality of anesthesia care rendered throughout the hospital, including surgical, obstetric, emergency, outpatient, psychiatric, and special procedures areas; develop regulations concerning anesthetic safety; and ensure evaluation of the quality of anesthesia care throughout the hospital.

The survey data show that input from the anesthesiology department concerning the administration of anesthetic drugs in the ED appears to be lacking more than 80% of the time in Wisconsin and Illinois (Figures 1–3). Whether this same percentage exists in the other states is unknown, but the probability is that the anesthesiology department participation in other states is also poor. Although response bias may exist in our results, the literature indicates that many EDs in the United States use these anesthetics (3–16) and do not believe that input from the anesthesiology department is needed (3–6). Anesthesiologists have expressed concern over the safe use of these drugs by nonanesthesiologists (17,18). Other authors believe that safety can be improved when patients are monitored while they are receiving anesthetic drugs (19–22). There is little information in the literature about the complication rate in the ED from the use of anesthetic drugs. Therefore, it would be difficult to assess the benefits of anesthesiology department participation in the ED. However, we believe this should not be used as an excuse to avoid participating in the evaluation of the quality and appropriateness of the use of anesthetic drugs outside the operating room.

The lack of larger anesthesiology department representation outside the operating room may be due to the lack of awareness of the widespread use of anesthetic drugs by nonanesthesiologists or to the lack of familiarity with the development of hospital policies and procedures to monitor these activities. Another possible reason for the reluctance of anesthesiologists to become involved is the fear that they will be held responsible for the action of physicians who function outside the department. At this time, there are no cases in the ASA Closed Claims Project (19,23–25) in which an anesthesiologist has been sued because of anesthetic drug administration by emergency department personnel (ASA Closed Claims Project, personal communication from F. W. Cheney, MD, July 19, 1991). However, as the JCAHO is advocating the active participation of anesthesiologists in monitoring and evaluating anesthetic care in hospital departments outside the operating room, neglecting this responsibility may put the anesthesiologist at risk for litigation problems in the future (26). Whatever the reason, the lack of anesthesiology department input in the development of criteria for monitoring and evaluating the quality and appropriateness of anesthetic drug use may have an adverse effect on patient care besides not fulfilling the recommendations of JCAHO or the ASA. By becoming involved with establishing the quality of anesthesia wherever it is given in the hospital, we will hopefully improve the quality of patient care and demonstrate to other specialties the anesthesiologists' ability to help with the issue of medical quality assurance outside the operating room.

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REVIEW ARTICLE

Airway Considerations in the Management of Patients Requiring Long-Term Endotracheal Intubation

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Oral vs Nasal Long-Term Endotracheal Intubation
Inability to Provide Leak-Free Ventilation
Endotracheal Tube Size
Changing the Endotracheal Tube and Problem Tracheal Extubations
Laryngotracheal Complications of Endotracheal Intubation
Tracheostomy: Why, When, and If
Care of the Patient With a Tracheostomy
Conclusion

Anesthesiologists are often consulted in the management of airway problems that occur outside the context of administering an anesthetic. Although many of these problems can be solved by applying the principles of airway management used in the operating room, other situations arise that require special considerations. This review addresses some of the factors that are important in the anesthesiologist's role as a consultant in airway management. These include not only considerations for endotracheal intubation, but also the special problems that arise in the maintenance of an airway of a patient whose ventilation is being mechanically controlled for a prolonged period of time (i.e., more than 1–2 days).

Oral vs Nasal Long-Term Endotracheal Intubation

Many of the acute factors that relate to the placement of endotracheal (ET) tubes in oral versus nasal locations are familiar to anesthesiologists. These factors, as well as complications of a more chronic nature, will help determine the route chosen for ET tube placement (Table 1). For anyone who has not had the misfortune of experiencing both, it is quite difficult to determine whether nasal is more comfortable than oral tracheal intubation. Although nasal tubes are believed to be more comfortable, an extensive study of prolonged intubation indicated that comfort was not a distinguishing factor between the two routes (1). From a nursing viewpoint, oral hygiene is more easily maintained with a nasal tube, but airway suctioning is not facilitated by either location and is usually more difficult through nasal tubes (1). The use of nasotracheal intubation obviates the need for a bite block or oral airway to prevent the patient from biting down and occluding the tube. On the other hand, patients with nasal tubes can swallow large amounts of air and suffer severe gastric distention (2). The nasogastric tube required to prevent such distention may also predispose to the development of a tracheoesophageal fistula (3). Tubes in either location may cause pressure necrosis at their respective sites of entry (e.g., nares or lips) such that careful taping and securing of the tubes (usually including extension of the tape behind and around the head) must avoid compression of surrounding tissues lest potentially disfiguring injuries occur (4).

More significant considerations in ET tube placement include the likelihood of accidental extubation and the development of sinus infection. A recent evaluation of the incidence of unintended extubations (i.e., by the patient) in a mixed medical-surgical intensive care unit (ICU) found no significant difference between patients who received oral or nasal tracheal intubation (5). However, oral ET tubes have less internal tube support and may be more susceptible to dislocations that are unrelated to self-extubation (6).

The association of maxillary sinusitis with nasotracheal intubation was first reported by Arens et al. in 1974 (7). More recent reports have provided further understanding of the problem. Paranasal sinusitis may occur in patients tracheally intubated electively for surgery or emergently (8). Patients who experience head trauma may be at particular risk as many have sinus air-fluid (blood) levels on initial computed tomography scans. These levels represent damage to the sinus and provide an excellent culture medium for bacteria (9). The incidence of sinusitis appears to increase dramatically after 5 days of nasal intubation

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Table 1. Considerations in Oral Versus Nasal Tracheal Intubation

	Oral	Nasal
Comfort	±	±
Suctioning	±	±
Oral hygiene	−	+
Lack of bite block requirement	−	+
Pressure necrosis of adjacent tissue	−	−
Stability	±	+?
Sinusitis	+	−
Ability to use larger tube	+	−
Laryngeal damage	−	+?

+, Clear advantage; +?, possible advantage; −, disadvantage; ±, indeterminate.

Table 2. Inability to Provide Leak-Free Ventilation

Incorrect cuff positioning
Tube size too small
Leak in balloon/valve system
Cuff leak
Tracheomalacia
Tracheoesophageal fistula

(10). Although the precise mechanism is not known, it appears likely that the ET tube may cause injury to the sinus ostia during insertion that results in edema with subsequent mechanical obstruction of the ostia. Diagnosis of sinusitis in the critically ill patient is best made by computed tomography scan, but purulent discharge in conjunction with standard radiographs or ultrasound may be adequate (11). These patients often have a previously unexplained source of fever. Treatment involves the removal of nasal instrumentation (including nasogastric tubes), its replacement with an oral ET tube, and the administration of antibiotics, at which time the anesthesiologist may be consulted if tracheostomy is not planned. Sinusitis in the critically ill patient is not to be taken lightly because of the resultant hypermetabolism and the risk of potentially serious intracranial infection. The latter is often refractory to antibiotics if the obstructing tube is not removed. The risk of sinusitis may justify the use of an oral rather than nasal ET tube when, in the judgment of the clinician, all other factors are equal.

The significance of endotracheal tube size in this setting will be discussed, but it is clear that an 8.0-mm-internal diameter (ID) ET tube cannot be passed through the nares and nasopharynx of all patients, and in some patients, even a 7.0-mm-ID ET tube (hereafter, 7.0 ET tube) cannot be passed. Therefore, the oral location may be preferred if a specific tube size is required, and the desired size nasal tube cannot be passed nasally. The larger internal diameter of the oral tube will produce less airflow resistance and offers the theoretical advantage of a reduction in the work of breathing. This resistance is further reduced because the oral tube may be cut shorter and because of the larger radius of curvature provided by the oral tube in situ (12).

A final important consideration is the alleged lower incidence and degree of laryngeal damage associated with nasal intubation (13). Nasal tubes may be somewhat more stable and therefore cause less movement-related injury to the larynx. In addition, the straighter positioning of a nasal ET tube entering the larynx (compared with an oral ET tube) may cause somewhat less pressure and therefore less damage to susceptible laryngeal structures. However, the most important factor may be simply the fact that smaller tubes are often used for nasal intubations.

Inability to Provide Leak-Free Ventilation

The anesthesiologist is often consulted to evaluate the patient in whom the ET tube cuff seal is not adequate (Table 2). This occurred in 11% of patients in the report by Stauffer et al. (1). If the patient is receiving adequate ventilation and is not in imminent danger of aspiration of gastric contents, the problem is not emergent. Leaks may involve a leak around the cuff as well as loss of air from the cuff system.

Incorrect positioning of the ET tube is probably the most frequent cause of leaks around the cuff. Generally, oral ET tubes are located acceptably if markings of 23 cm and 21 cm appear at the upper teeth in men and women, respectively (14). For nasal intubations, approximately 3 cm additional distance is required for proper positioning at the nares. These depths of insertion usually make endobronchial intubation unlikely and should therefore be examined initially to ensure a reasonable depth of placement (15). Extremely tall patients may require adjustments based on radiographic location of the ET tube. The distance between the vocal cords and the carina in adults varies between 10 and 14 cm, largely because of differences in tracheal length (16,17) (Figure 1). If the tip of an 8.0 ET tube is placed 3–4 cm above the carina, to avoid endobronchial intubation, the distance from the tube tip to top of cuff is usually about 5 cm but may vary slightly with different manufacturers. This leaves a variable 1–6-cm distance between the top of the cuff and the vocal cords. If the cuff protrudes above the cords, a leak may develop in spite of very large cuff volumes. Although laryngoscopic examination (either direct or fiberoptic) is usually required to identify this situation, occasion-

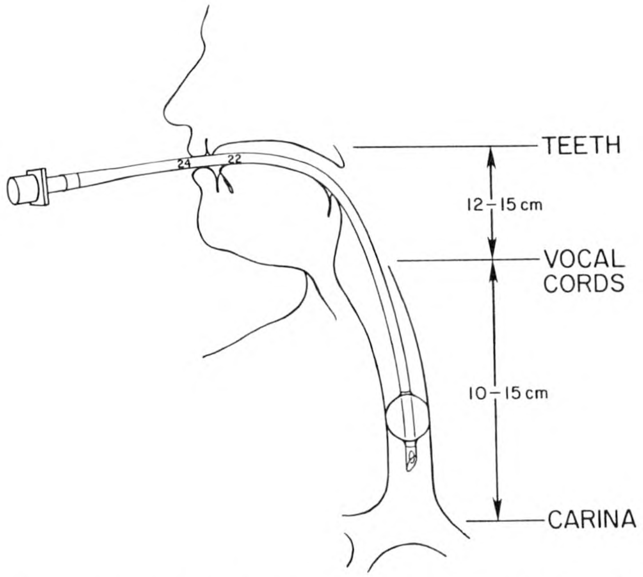

Figure 1. Diagrammatic representation of key distances relating to ET tube positioning.

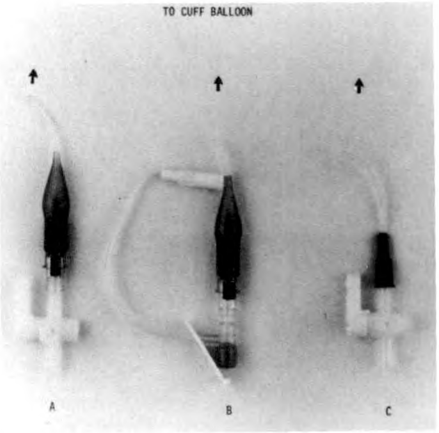

Figure 2. Suggested means for sealing leaks in pilot balloon valve via **(A)** three-way stopcock and **(B)** "T-connector" or for sealing leaks in pilot balloon via **(C)** insertion of 22-gauge catheter directly into cut end of pilot tubing. (Reprinted with permission from Watson E, Harris MM. Leaking endotracheal tube. Chest 1989;95:709.)

ally the top of the cuff can actually be seen on simple inspection of the oropharynx. Eccentric cuff inflation can also cause a leak and should be prevented by inspection of the inflated cuff before insertion (18).

Varying leaks owing to small ET tubes are seen daily in pediatric practice. In the adult, a leak owing to a small tube is less likely but still possible, especially if a 7.0 ET tube is inserted into very large or highly compliant airways such as might be encountered in the emphysematous patient. These highly compliant airways enlarge to a greater extent in the presence of applied pressure (T. J. Gal, personal communication). In this situation, very high cuff volumes may be required to seal the airway, and the "low-pressure" characteristics of the cuff may be exceeded, resulting in excessive pressures on the tracheal wall.

Leaks may commonly develop in the inflation valve and pilot balloon system for cuff inflation. If a valve leak is detected, a three-way stopcock or T-connector can simply be inserted to maintain a seal. If the valve housing or pilot balloon is leaking, the connecting tubing can be cut and an alcohol-lubricated 22-gauge catheter can be inserted into the tubing. A T-connector or three-way stopcock can then be attached to maintain a seal (19) (Figure 2). Cuff leaks detected immediately after intubation are usually due to a nick made by teeth, nasal turbinates, or Magill forceps. Esophageal intubation must also be ruled out quickly in the case of all leaks immediately following tube insertion. Late occurring leaks are much more common in the inflation valve system than in the cuff. The body of the cuff is likely to be leaking if kinking or compression of the connecting tubing after cuff inflation does not seal the leak. Normally, when the cuff is fully deflated, a negative pressure can be felt with the deflating syringe, and this "tug" is lost when cuff integrity is lost. In addition, the normal resistance to complete inflation is absent and the cuff is not palpable in the suprasternal notch or visible on radiograph. A true cuff leak will generally require a tube change unless extubation is imminent. If changing the tube is judged to be unacceptably dangerous, tracheostomy may be considered. A continuous-flow apparatus for temporary inflation of a leaking cuff has recently been described and could be used as a stop-gap measure (20).

Serious structural complications of intubation (or tracheostomy) that can result in lack of airway seal include tracheomalacia and tracheoesophageal fistula. Tracheomalacia involves weakening of the tracheal cartilage just above and at the level of the cuff. While the airway remains instrumented, widening of the trachea may occur and requires progressive increases in cuff volume to seal the airway. These two complications are discussed in more detail in a later section.

Endotracheal Tube Size

The choice of ET tube size is of concern to the consultant for several reasons. First of all, if the tube is too small, higher cuff pressures will be required to prevent gas leakage, and this may result in converting the low-pressure cuff into one of relatively high pressure. If the tube is too large, folds may be produced in the underinflated cuff and allow for channeling and aspiration of material from the pharynx (21).

Fiberoptic bronchoscopy has become a widely used diagnostic and therapeutic modality in the ICU (22). Most flexible bronchoscopes designed for adult use have a 4.9-mm outer diameter (OD), although some may have a 6.0-mm OD (23). When a 4.9-mm OD bronchoscope (approximately 19 mm^2 in cross-sectional area) is inserted into a 7.0-mm ET tube (approximately 38 mm^2 in area), a cross-sectional area nearly equivalent to a 5.0 ET tube remains for ventilation around the tube. Many bronchoscopists believe that the difficulty in ventilation and the potential for auto-positive end-expiratory pressure and hyperinflation with a 5.0-mm OD scope make bronchoscopy unsafe through a 7.0 ET tube. When inserted into an 8.0 ET tube, the same scope allows for an airway approximately equivalent in cross-sectional area to that of a 6.0 ET tube. For this reason, bronchoscopists frequently request that a 7.0 ET tube be replaced with a larger tube for bronchoscopy. This poses several problems, including the risks associated with a single or multiple reintubation(s) if the larger tube is subsequently replaced with a smaller tube. The latter may be desirable, for example, in smaller female patients in whom the larger tube (8.0 mm ID) may present an increased risk of laryngeal injury (24). When consulted for this purpose, the anesthesiologist must judge whether the risks justify the benefits. This requires the consultation of the bronchoscopist, preferably in a note written in the patient's chart. Alternatives to changing the tube include (a) performing the bronchoscopy through the 7.0 ET tube with careful monitoring for acceptable oxygenation and ventilation and modification of ventilatory settings or ventilation by hand to achieve an acceptable respiratory status; (b) using a smaller bronchoscope. (There are pediatric bronchoscopes that should be long enough for most purposes [23]); (c) inserting the bronchoscope though the glottis anteriorly to the ET tube to attain access to the tracheobronchial tree (25). (This requires skill and cooperation on the part of the bronchoscopist and may fail in patients with very low compliance or high resistance because a sizeable leak can occur.); (d) initially intubating all patients with an ET tube of at least 7.5-mm ID (our current approach). There is a small possibility that this may increase the risk of laryngeal stenosis in patients with an unusually small larynx. If the consultant anesthesiologist determines that the risk of changing the ET tube is unacceptable and the bronchoscopist cannot work through or around the existing tube, tracheostomy can be considered.

The inner diameter of the ET tube is also an issue in weaning from mechanical ventilation because of the potential increased work of breathing. There is no question that breathing is more difficult through smaller ET tubes. At issue here is the level at which this increased work of breathing achieves clinical significance. Shapiro and coworkers (26) demonstrated that volunteers, breathing through ET tubes placed in the pharynx, reached tension time indices at high minute ventilations that would result in diaphragmatic fatigue with 6.0 and 7.0 ET tubes but not with larger ones. The tension time index (TTI) is the product of the inspiratory time or duty cycle (T_I) relative to the entire breathing cycle (T_{TOT}) and the mean transdiaphragmatic pressure (P_{di}) expressed as a percentage of the maximum transdiagphragmatic pressure ($P_{di\ max}$). Thus TTI = $T_I/T_{TOT} \times P_{di}/P_{di\ max}$. If TTI > 0.15, i.e., T_I/T_{TOT} and $P_{di}/P_{di\ max}$ are both 0.4 or more, fatigue is likely. Another study that examined the work per minute of breathing through isolated ET tubes indicated approximately 50% higher values for a 7.0 ET tube compared with a 8.0 ET tube at a respiratory rate of 20 breaths/min and a tidal volume of 500 mL (27). An extension of this work with isolated ET tubes also examined the additional added work of breathing through a ventilator demand valve system for continuous positive airway pressure (CPAP) (28). These workers noted that at a tidal volume of 500 mL and respiratory rate of 25 breaths/min, as often observed in a patient after discontinuing mechanical ventilation, total inspiratory work per liter was increased from 0.06 kg·m (0.1 kg·m = 1 joule) for an 8.0 ET tube to 0.07 kg·m for a 7.0 ET tube (both with CPAP/ventilator system). For a 12.5-L minute ventilation, this would be 0.75 kg·m/min compared with 0.88 kg·m/min, or approximately an 18% increase. Converting to watts (1 watt = 6.3 kg·m/min), this represents 0.12 W and 0.14 W for the respective tube sizes. Proctor and Woolson (29) have reported that the normal work of breathing in young healthy men is 0.07 W (0.44 kg·m or 4.4 J). They determined that a work of breathing of 0.41 W (2.50 kg·m/min) distinguished between postoperative patients who did or did not require continued ventilation. In postoperative patients, Peters et al. (30) found that less than 10% of patients capable of sustaining ventilation had a work of breathing greater than 0.4 W. More recent work indicates that an (inspiratory) work of breathing of less than 1.6 kg·m/min was necessary for successfully discontinuing ventilation (31). It would appear, then, that the increased work of breathing going from a 8.0 ET tube to an 7.0 ET tube is hardly excessive and accounts for only a small proportion of the increase seen in patients in whom mechanical ventilation is discontinued. In fact, failure to tolerate the small degree of added work required to breathe successfully through a 7.0 ET tube may indicate that the patient is likely to fail extubation because of inability to cope with added stresses, such as secretions and atelectasis. If there is concern that a 7.0 mm ET tube is inhibiting the patient's ability to breathe spontaneously, the provision of a small amount of pressure support ventilation can overcome the work of breathing through the ET tube as well as that increase in work added by other devices such as demand valves (28). The exact amount of pressure support required depends on the inspiratory flow rate and the demand valve system for CPAP. For example, with a 0.5-L/s flow rate and the CPAP system with the Puritan-Bennett 7200 ventilator, 6 cm H_2O for the 8.0 ET tube and 10 cm H_2O for the 7.0 ET tube should compensate for the additional work of breathing (28).

One additional consequence of smaller ET tube size is the possibility of developing "auto-PEEP" and hyperinflation (32). This phenomenon is only likely to develop when extremely high levels of ventilation and obstructive airway disease are present in conjunction with the use of a 7.0 (or smaller) ET tube. If ventilation cannot be reduced, the degree of auto-PEEP can only be minimized by increasing the time available for expiration. This is best accomplished by decreasing respiratory rates but may also be enhanced by increased inspiratory flow rates with their attendant reduction in inspiratory time (33).

Changing the Endotracheal Tube and Problem Tracheal Extubations

The ET tube may require changing for a variety of reasons. The issues of cuff leak, tube size requirement for bronchoscopy, and the work of breathing have been discussed. The nasal tube may be changed to an oral tube if treatment of sinusitis is necessary. On occasion, intensivists may request changing an oral tube to a nasal tube for some of the reasons previously discussed including comfort and stability. Before changing the tube, the consultant anesthesiologist should carefully consider the need for the change, consider alternatives, and discuss risks with the consulting service, and even with the patient or family if the risk is considerable. The possibility of tracheostomy should be considered at this time. Risks of tube changing include inability to reintubate the trachea, aspiration, the rapid onset of hypoxemia in patients requiring high levels of positive end-expiratory pressure, laryngospasm, and the mechanical problems of any intubation, e.g., tooth breakage and esophageal intubation. It is essential to have all equipment present (bag O_2, mask, oral airways, suction) and not assume that such equipment will be immediately available.

The ET tube can be changed under direct laryngoscopic vision using Magill forceps, nerve blocks, topical anesthesia, and minimal or no sedation (34). It is preferable to remove the old tube under direct vision while maintaining adequate visualization of the glottis throughout the procedure. The curved Macintosh blade may better facilitate exposure of the "crowded" glottic area and allow more room to maneuver. Adequate pharyngeal suctioning should precede all of these tube changing or removal maneuvers. A vagolytic drug (e.g., glycopyrrolate, 0.2 mg IV) may be used to minimize secretions and, therefore, the likelihood of bronchospasm. Alternatively, an intravenously administered anesthetic and muscle relaxant may be used if it is reasonably certain that laryngoscopy and reintubation of the trachea can be readily accomplished. The use of heavy sedation and muscle relaxants should be reserved for special situations when conscious reintubation presents extraordinary difficulties (e.g., severely psychotic, uncooperative, or retarded patients, and patients with severe movement disorders).

An alternative means of changing the tube is to use a mechanical device such as a stylet. A nasogastric (NG) tube may be used, but its flexibility may result in difficult tube entry into the larynx because the pliable NG tube may enter the periphery rather than the center of the glottis. This may cause the ET tube tip to become impacted on the epiglottis or, more commonly, on the posterior commissure of the glottic aperture. Turning or flexion of the neck, in combination with rotating the ET tube from 90° to 180°, may allow passage. The use of a hook made from an intubating stylet or of the Magill forceps may aid manipulation of the NG tube into a position that facilitates intubation. Cooling the NG tube increases its rigidity and may also aid intubation (35). The Eschmann introducer, a more rigid device available in several sizes, is a more reliable tube changer in our experience than the NG tube (Figure 3, Eschmann Health Care, West Sussex, England). Care must be taken not to damage the fragile tracheal mucosa with this relatively rigid stylet. This introducer can also be used as a stylet to facilitate blind oral intubation and to ascertain tube location by careful insertion down to the carina where resistance is usually felt. These blind stylet techniques are not completely dependable and can result in loss of the airway. For example, it may be impossible to insert the new tube into the larynx. Use of a smaller ET tube size, such as 6.0 mm ID, may be very helpful when this happens. Bedger and Chang (36) have designed a "jet-stylet" ET catheter to allow for gas delivery and suction during blind ET tube changes in patients with compromised upper airways (Figure 4). These authors used a 65 cm length of polyethylene tubing with a 4.5-mm OD. A removable 15-mm adapter is used for connection to the anesthesia machine, jet ventilator, or other gas sources. A 5.0-mm ID or larger ET tube is passed over this tubing into the trachea as for the aforementioned stylet techniques. The authors report that all attempts

Figure 3. The Eschmann introducer, a moderately rigid stylet used in ET tube replacement.

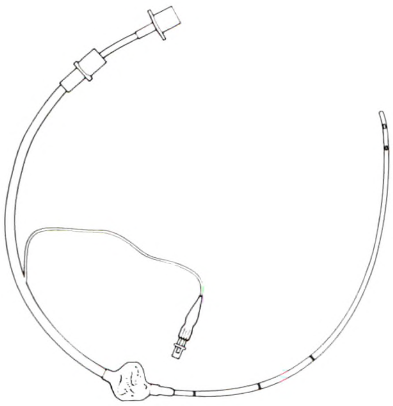

Figure 4. Jet stylet catheter placed through a 5.0-mm ET tube demonstrating distal side ports and circumferential marks at 20, 25, and 30 cm to assist in positioning. The proximal 15-mm adapter is detachable for advancing and removing the ET tube. (Reprinted with permission from Bedger RD, Chang J-L. A jet-stylet endotracheal catheter for difficult airway management. Anesthesiology 1987;66:221–3.)

at using this device had been successful up to the time of the report.

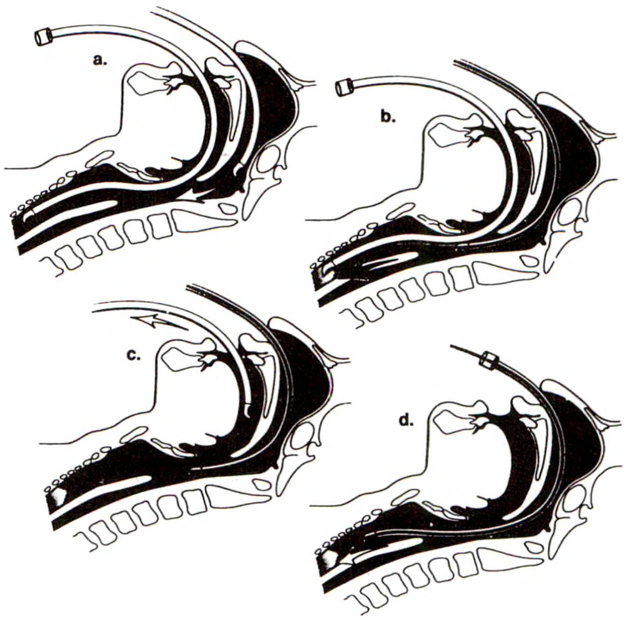

Figure 5. Endotracheal tube changing with the fiberoptic bronchoscope demonstrating one technique for changing an ET tube, in this case an oral tube, to a nasal tube. The new ET tube is placed into the posterior pharynx **(a)**. The patient's pharynx is vigorously suctioned, the current ET tube cuff is deflated, and the fiberoptic bronchoscope is passed into the new ET tube. The fiberoptic bronchoscope is advanced through the new ET tube and inserted into the trachea, outside the current oral ET tube, to the level of the midtrachea **(b)**. After suctioning, the current oral tube is withdrawn **(c)** and the new ET tube is advanced using the bronchoscope as a stylet **(d)**. (Reprinted with permission from RP Dellinger. Fiberoptic bronchoscopy in adult airway management. Crit Care Med, 18, 882–7, © by Williams & Wilkins, 1990.)

When equipment and skilled operators are available, the flexible fiberoptic bronchoscope can be used to change the ET tube. After placing an ET tube over the bronchoscope, the scope is placed alongside the ET tube to be replaced, the cuff is deflated slightly and the tip is inserted well into the trachea (37–39) (Figure 5). The old tube is removed and the new tube is threaded into the trachea. Some maneuvering of the neck, tube, and/or scope may be required on occasion to allow for transglottic passage. This technique allows for conversion of a nasal ET tube to an oral one and vice versa. If the bronchoscope cannot be passed alongside the ET tube in the larynx, the first tube can be removed under direct fiberoptic vision and the bronchoscope subsequently can be inserted into the larynx (Figure 6). This technique is not as certain a means of securing the airway. Another technique described by Hudes et al. (40) allows for changing tubes from nasal to nasal and oral to oral only. In this method, a new ET tube is placed over the bronchoscope which is inserted into the original ET tube after removing the 15-mm connector. Using a No. 11 scalpel blade pointed away from the bronchoscope, the old tube is cut away as it is withdrawn until it can be completely removed and the new ET tube inserted. Although the authors accomplished this in 20–30 s, we have found this a little more difficult and time-consuming but still a reasonable option in the difficult airway situation. As with all bronchoscope techniques, proper placement is instantly checked. Suction is available through the bronchoscope, and the insufflation of oxygen through the side port makes any bronchoscope an instant "jet-stylet." This technique may be difficult to use with a 7.0 ET tube unless a 4.9-mm OD or smaller bronchoscope of adequate length is available. We have found that the use of small pliable pediatric bronchoscopes for adult ET tube placement is fraught with difficulty and often results in damage to the bronchoscope.

In addition to ET tube changes, safe tracheal extubation of the patient with upper airway burns or trauma or head and neck surgery may present a clinical dilemma. The presence of a leak when the cuff is deflated is an encouraging but not entirely predictive sign of airway patency after extubation. The absence of a leak in this situation is not a contraindication to extubation but is another indicator that there may be little reserve in the caliber of the upper airway owing to the presence of edema. To maintain access to the airway and oxygenation if necessary, the jet-stylet catheter may be used for a trial of extubation

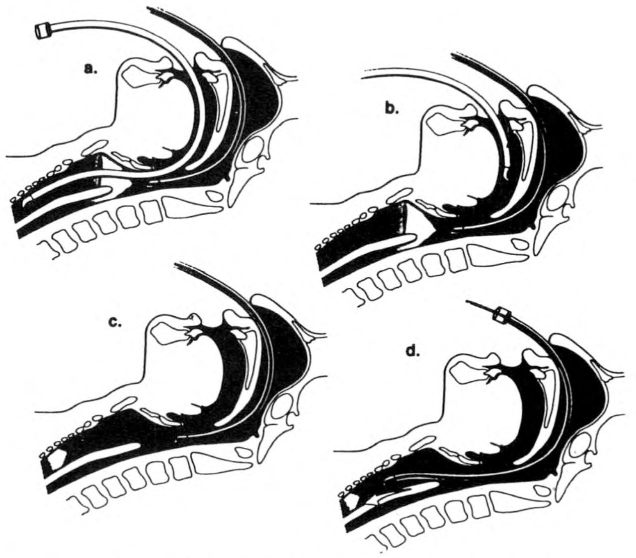

Figure 6. Endotracheal tube changing with the fiberoptic bronchoscope, demonstrating an alternative technique for changing an ET tube, in this case an oral tube, to a nasal ET tube. This technique differs in that, if the fiberoptic bronchoscope cannot be passed outside the existing ET tube, the fiberoptic bronchoscope is positioned above the vocal cords **(a)** and the tube to be replaced is removed **(b)**. The fiberoptic bronchoscope is then advanced into the trachea **(c)** and used as a stylet for advancement of the new ET tube **(d)**. (Reprinted with permission from RP Dellinger. Fiberoptic bronchoscopy in adult airway management. Crit Care Med, 18, 882–7, © by Williams & Wilkins, 1990.)

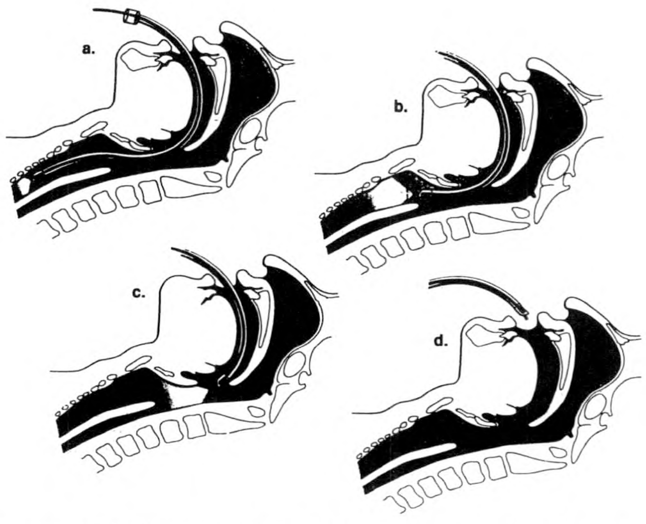

Figure 7. Tracheal extubation facilitated by use of a fiberoptic bronchoscope. The fiberoptic bronchoscope is inserted through the ET tube until it is positioned just past the tip of the ET tube. The two are then withdrawn in tandem using the bronchoscope to inspect the airway during withdrawal. If findings compatible with upper airway obstruction are noted, the diagnosis is made and the tube is reinserted, using the bronchoscope as a stylet. If no evidence of upper airway obstruction is noted, then the two are withdrawn totally. (Reprinted with permission from RP Dellinger. Fiberoptic bronchoscopy in adult airway management. Crit Care Med, 18, 882–7, © by Williams & Wilkins, 1990.)

(36). A rigid stylet such as the Eschmann introducer can maintain access to the airway but does not allow for suctioning or oxygen administration. The bronchoscope can also be used as an extubation stylet and possesses the added advantage of diagnostic capability (39) (Figure 7). When possible, any tracheal extubation of extreme risk should be performed in the operating room with personnel available who are capable of rapidly establishing a surgical airway.

Laryngotracheal Complications of Endotracheal Intubation

The laryngotracheal complications of prolonged intubation have been the subject of several recent reviews and will only be discussed briefly, especially with respect to some newer observations (4,24).

Several points of the excellent review by Bishop et al. (24) require reemphasis. The laryngeal complications of endotracheal intubation result from the pressure generated by the round ET tube at three locations: the cricoid cartilage and the two vocal processes of the arytenoids. Injury at these sites is probably exacerbated by movement of the tube against the larynx during neck flexion and extension, inspiration, cough, and swallowing. The smaller larynx of women appears to predispose them more to laryngeal injury and subsequent stenosis. The ratio of ET tube outer diameter to larynx size may be the major factor contributing to injury in this case. Anesthesiologists are well aware of acute postextubation problems such as edema at various sites within the larynx as well as laryngospasm and hoarseness. Inability to protect the airway for some time after long-term intubation may also be a serious problem (41). Swallowing disorders arising after prolonged intubation may contribute to a situation in which all patients should be fed initially with extreme caution (42). Severe pain in the laryngeal area may suggest a retrocricoid abscess requiring drainage and antibiotics (4). Whereas persistent hoarseness and granuloma formation are serious sequelae of chronic intubation, laryngeal stenosis is perhaps the life-threatening complication that represents the most compelling reason to replace an ET tube with a tracheostomy.

The review by Bishop et al. (24) cites a 0%–1% incidence of ET tube-related laryngeal stenosis, but the actual incidence is unknown because case reports may not include the entire scope of the susceptible population. Since that publication, new and contradictory data have become available. In a study often cited by colleagues in otorhinolaryngology, Whited (43) studied 200 patients who had their tracheas intubated for various lengths of time. Patients whose tracheas were intubated for 2–5 days had mild reversible posterior endolaryngeal edema. In a second group whose tracheas were intubated for 6–10 days, there was a 5% incidence (5/100 patients) of chronic laryngeal stenosis, including four cases of extended complex stenosis. Of 50 patients whose tracheas were intubated for 11–24 days, there were six with chronic laryngeal stenosis, all of an extended complex nature. These six patients had each undergone tracheostomy after the period of intubation. Two were left with permanent tracheostomies, and the other four underwent lengthy and extensive reconstructions before decannulation could be accomplished. Unfortunately, patient gender and ET tube size were not noted in this study. In contrast, Colice and his colleagues (44) studied 54 male patients whose tracheas were intubated for longer than 4 days and noted that significant chronic laryngeal stenosis developed in none of the patients. This study reported that laryngeal damage, particularly swelling, was noted to develop after performance of tracheostomy but was not affected by the length of intubation or the ratio of ET tube to laryngeal size. This increase in laryngeal damage may be related to increased bacterial access after the performance of tracheostomy (45). An additional factor may be the cessation in vocal cord movement, with subsequent scarring and stricture formation of the inflamed posterior larynx after ET tube removal (46). It is important to note that the patient population studied by Colice et al. in a Veterans Administration Hospital included no women and few young, previously healthy patients (44). Therefore, it is difficult to reconcile these two conflicting studies and arrive at a clinically reasonable approach to minimizing laryngeal injury (43,44). Although, experimentally, the area of mucosal ischemia has been shown to be related to ET tube size, there is no clinical evidence that the size of ET tubes in current clinical use has any impact on eventual laryngeal injury (47). Overall, the problem does not appear to be of the magnitude and frequency described by Whited (1,4,24).

Tracheal injuries have been markedly reduced by the use of high-volume, low-pressure cuffs on both ET tubes and tracheostomy tubes (48,49). Much credit should be given to the pioneering work of Grillo and colleagues at the Massachusetts General Hospital (50). Tracheal dilation noticeable on chest radiograph is often the first sign of injury to the cartilaginous rings and appears to be the result of pressure necrosis at the cuff site (51). An enlarging cuff-to-tracheal diameter ratio that reaches or exceeds 150% may be predictive of eventual severe stenosis at the cuff site (52). The first step in management includes an attempt to provide adequate ventilation with the cuff inflated to pressures of 25 mm Hg or less. Cuff pressures should be measured throughout any prolonged period of ET intubation or use of a cuffed tracheostomy tube. Estimation of cuff pressure by finger palpation is not adequate for this purpose (53). In addition to the possibility of inadequate ventilation because of cuff leak, an underinflated cuff may predispose to aspiration (54,55). Because protection against aspiration of gastric contents requires cuff pressures of at least 20–25 cm H_2O, quantitation of pressures is required to tread the fine line between mucosal ischemia (pressures greater than 30 mm Hg) and inadequate airway protection (24). A ventilator-delivered inspiration will transiently increase cuff pressures to approximately the level of airway pressure, so that tracheal mucosal perfusion may be limited to exhalation if these pressures are sufficiently high (47). In addition, spontaneous inspiration may transiently widen tracheal diameter leading to inadequate cuff seal (56). The conventional method of injecting air via a three-way stopcock may give a falsely low pressure reading but is probably adequate if performed consistently with the presently available cuffs (57). The success of the conventional high-volume, low-pressure cuffs in making serious cuff-related injuries a rarity has obviated the need for more complicated devices that have been designed to control cuff pressure (e.g., the Lanz-type cuff).

As noted previously, tracheomalacia may be the first sign of tracheal damage. This is generally more of a problem as a precursor to an eventual site of stenosis than as primary problem per se. However, continued widening of the trachea may occasionally result in marked difficulties in producing an adequate seal with the cuff. Various approaches to this problem include advancement of the tube to a different site in the trachea or replacement with a larger ET tube that occupies a greater part of the tracheal diameter and usually results in a better cuff seal but may increase the risk of laryngeal damage. Other therapeutic possibilities are use of an ET tube with the large, low-pressure foam-filled cuff introduced by Kamen and Wilkinson (Bivona Surgical, Hammond, Ind.), or tracheostomy using an armored tube that can be repositioned in the trachea with an adjustable collar on the flange of the tube (Rusch, Inc., New York, N.Y.) (58,59). Also, the need for a cuff may be obviated if the patient can be successfully ventilated at low pressures with some form of high-frequency ventilation. This may represent an alternative in institutions that have experience with this technique.

Some degree of tracheal stenosis at the cuff site is quite common; but severe, functionally limiting stenosis at this site is very uncommon in the present era of the low-pressure cuff. Diagnosis involves simple tracheal radiographs, fluoroscopy, and endoscopic examinations (60). In the study by Stauffer et al. (1), 3 of 27 patients had stenosis at the cuff site. In all these patients, tracheal diameter was reduced less than 50%, a degree of narrowing likely to be asymptomatic. The normal adult tracheal diameter of

14–16 mm allows for a great reserve in the face of such stenosis. Another study reported a similar degree of cuff site stenosis (25%–30%) and incidence (2 of 19 patients) with intubation for longer than 24 h (61). Tracheal stenosis at the site of the tracheostomy stoma, on the other hand, appears to be more common and more severe (1).

As noted earlier, tracheoesophageal fistula may present as a cuff leak unresponsive to the usual therapeutic measures including ET tube replacement. This is a rare complication of ET intubation and is relatively more common after tracheostomy. Risk factors include high cuff and airway pressure, motion of the tube, length of intubation, nasogastric tube presence, and use of steroids (3). Tracheal necrosis associated with infection in the tracheoesophageal space may result in a massive fistula (62). In addition to cuff leak, these patients may manifest an increase in secretions as well as evidence of repeated aspiration. Diagnosis involves demonstration of the fistula via tracheoscopy and cine-esophagography (63). Therapy includes placement of the ET tube (or tracheostomy) with the cuff below the fistula if continued ventilation is required, removal of NG tube(s), aggressive nutrition and treatment of infection, and discontinuing ventilation as soon as possible (64). High-frequency ventilation may be helpful if conventional ventilation is difficult or impossible (3). Surgery may be best delayed until ventilatory support is no longer required but may be needed earlier if the side-effects of the fistula cannot be controlled (63).

Tracheostomy: Why, When, and If

Although the vast majority of physicians in critical care areas maintain an internal clock with respect to the allowable duration of ET intubation before tracheotomy is "indicated," medical justification for a defined time period is elusive. As identical high-volume, low-pressure cuffs are used on both devices, the debate weighs the laryngeal complications of ET intubation against the surgical and stoma-related complications of tracheotomy. (Note that tracheotomy, the operation, derives from the Greek work for "incision," whereas tracheostomy derives from the word for "mouth" and may refer to the opening in the trachea or the formation of the opening.) As previously noted, the problem of laryngeal injury is not solved by, and may be exacerbated by, the performance of tracheotomy after the usually accepted 7–21-day period of intubation (44). This may arise from the fact that laryngeal injury peaks in severity before day 7, and very early tracheostomy insertion would be required to avoid the possible injury (65). Studies that attempt to predict the need for long-term intubation may, in fact, be overlooking this earlier critical period for the development of trauma to the larynx (66).

The lack of a clear-cut medical advantage to tracheostomy does not mean that the procedure should not be performed for long-term ventilatory care (Table 3). Limitations on critical care resources result in a requirement for maintenance of stable ventilated patients outside of the intensive care unit, so that more critically ill patients can be admitted and cared for. The tracheotomized patient with a well-formed tract or other method to maintain the early stomal tract (e.g., Bjork flap or sutures attached to the trachea) is more safely cared for in the standard nursing unit than is an intubated patient because the displaced tracheostomy tube can be replaced by personnel unskilled in airway management (67). Patients who may require periods of ventilation interspersed with reasonably long times off the ventilator (e.g., patients with myasthenia gravis) can benefit from the maintenance of a tracheal stoma with various button devices, uncuffed tubes, or fenestrated tubes (68). Finally, there may be distinct subsets of patients, such as diabetic females, who do have an inordinately high risk for ET tube-related laryngeal injury and who should be considered for early tracheostomy placement (69).

It is becoming increasingly evident that in the general population, a specified "safe" period of 1–3 wk of tracheal intubation before the required performance of a tracheostomy is not well substantiated (70). A patient who does not receive a tracheostomy during the first week of intubation may subsequently undergo cannulation for reasons specific to that patient's situation rather than because a specific time period has elapsed. The added cost of inserting a tracheostomy ($2000–$3000 dollars at the Mayo Clinic in 1988) will become a more important factor in the decision-making process (71).

The risk of the actual operative procedure appears to be acceptably low in adults, with one group reporting no perioperative mortality or major morbidity in 81 patients (72). Other studies have reported some degree of perioperative morbidity (1,67). There are several potential disadvantages to the presence of a tracheostomy. It has been reported that pulmonary aspiration is a greater problem with tracheostomy than with ET intubation (73). A higher incidence of respiratory infection in the tracheostomized patient may be due to aspiration or to a higher incidence of tracheobronchial colonization (74). This fear of pneumonia has particularly discouraged the placement of a tracheostomy tube in burn patients, although these patients may actually fare no worse than others in this regard (75). Some clinicians are reluctant to place a tracheostomy tube in patients after surgical procedures that may have interrupted tissue planes (e.g.,

Table 3. Tracheostomy Versus Tracheal Intubation

	Tracheostomy	Intubation
Advantages	Ease of replacement (once tract has formed)	Rapid insertion by skilled consultant in most settings
	Speech, mobility, and swallowing enhanced	Lack of need for surgical procedure (risk, expense)
	Patient can be nursed outside of ICU	Lack of stomal complications
	Ease of suctioning?	
	Patient comfort?	
Disadvantages	Complications at cuff site	Complications at cuff site
	Stomal complications	Laryngeal complications
	Possible contribution to ultimate laryngeal injury	Replacement requires skill at all times
	Tracheo-innominate artery fistula formation	Generally requires ICU level supervision
	Possible increase in pulmonary infections	Injuries at nose or mouth
	Access to mediastinum by infectious agents after local surgery	
	High mortality for inadvertent decannulation before tract formation	

ICU, intensive care unit.

cardiac surgery) and that theoretically facilitate entry of colonizing pathogens into the mediastinum.

Tracheo-innominate artery fistula is an important but uncommon complication that seems to be limited to tracheostomized patients, probably because of the stiffer tube tip. The classic presentation involves tracheal bleeding and pulsation of the tracheostomy tube usually noted more than 24 h after placement of the tube. Diagnosis should be aggressively approached with endoscopy, arteriography, or even wound exploration. Emergency management includes further inflation of the tracheostomy balloon and, if necessary, digital compression of the artery via an incision in the suprasternal notch until definitive surgery can be performed. Although a low tracheostomy site may be to blame, the problem may occur with properly placed tubes when the artery is abnormally located (76).

Finally, the patient who is hemodynamically unstable, requires high levels of positive end-expiratory pressure, or who is receiving any of the currently popular unconventional modes of ventilation associated with high mean airway pressures (e.g., pressure control ventilation with inverse inspiratory-to-expiratory ratio) should probably not be transported to an operating room for tracheostomy because it is difficult to maintain the required level of constant support. In fact, there is probably little reason to perform tracheostomy on these high-risk patients unless their condition improves. Tracheostomy for long-term airway management is an elective procedure under most circumstances. Exceptions would include patients in whom the ET tube must be urgently replaced but in whom reintubation is judged unacceptably hazardous. One alternative involves tracheostomy in the ICU with carefully selected patients. Although some surgeons perform elective tracheotomy in the ICU, others prefer to utilize the operating room because of greater resources for dealing with such rare complications as massive hemorrhage or loss of the airway. Finally, newer approaches to airway management such as CPAP by mask combined with minitracheostomy may eventually replace our current techniques (77). It should be reemphasized that the decision to replace an ET tube with a tracheostomy is a difficult one and must be individualized based on the available facts and medical judgment rather than on an arbitrary time limit (78).

Care of the Patient With a Tracheostomy

Without direct participation in intensive care medicine, the anesthesiologist may have minimal contact with patients after tracheostomy is performed. Important complications associated with the procedure itself include bleeding, loss of the airway, pneumothorax, and tension pneumomediastinum. In the operating room, it is essential that the ET tube not be removed from the larynx until intratracheal placement of the tracheostomy tube is certain. The tube may enter tissue planes lateral or anterior to the trachea or perforate the back wall of the trachea to enter the esophagus. The tube may also be dislodged after initial placement: This is more likely with uncuffed tubes. Tracheostomy tube changes required in the week after surgery should be performed with the knowledge that a tracheocutaneous tract may not yet be reliably formed, and that removal of the tube can result in loss of the airway. It is best to change the tube over a tube exchanger with equipment for ET intubation immediately available. The search for the trachea after inadvertent decannulation may be facilitated with the use of a laryngoscope with a small straight blade (e.g., Miller 1). If necessary, oral intubation should be used to reestablish the airway (unless a tracheostomy was performed because oral intubation was not possible.) Decannulation before tract formation has up to a 25% mortality and can be lessened by the aforementioned use of a "U"-shaped Bjork flap or externally placed sutures attached to the trachea (67).

The problems of speech and weaning (including stomal maintenance) are addressed in more detail in a recent review (68). Special tubes or buttons used in the subacute or chronic care setting are best replaced with conventionally cuffed tracheostomy or wire-reinforced ET tubes in the operating room to provide anesthetic care. Special extra-long tracheostomy tubes for anatomically variant patients are also available (Portex, Inc., Wilmington, Mass.; Shiley, Inc., Irvine, Calif.). Details of the everyday practical care of the tracheostomized patient are well covered in brochures available from tube manufacturers. These problems include the need for humidity, suctioning, wound care, and maintenance of a fully patent airway, usually by frequent (every 3–4 h) cleansing of the inner cannula.

Conclusion

The anesthesiologist's practice of airway management is not confined to the operating room but extends to the consultant care of the airway in other settings. Many individuals use a variety of approaches to these problems and there is likely to be a great wealth of clinical information and "pearls" that are not published in the literature. In this review, however, we have attempted to bring together a diversity of published material in addition to our own clinical experience to synthesize an approach to these problems that are not well addressed in currently available sources.

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Effect of Cardiopulmonary Bypass on Plasma Cyclosporin A Levels in a Renal Transplant Patient

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Cyclosporin A (CsA) is a potent immunosuppressant that has contributed significantly to organ survival after transplantation surgery (1). Several studies have established a relationship between blood CsA levels necessary to minimize postsurgical organ rejection and higher levels that are associated with nephrotoxicity (2–7).

The blood levels of many different categories of drugs change during cardiopulmonary bypass and the postbypass period (8–11). We report a case of a renal transplant patient receiving continuous CsA therapy who underwent coronary artery bypass grafting during which CsA levels were measured.

Case Report

A 54-yr-old, 75-kg man was admitted with a recent history of unstable angina and was scheduled to undergo coronary artery bypass grafting. His past medical history was significant for polycystic kidney disease for which he received a renal allograft transplant in 1985. His medications included CsA (400 mg), which he had been taking since his transplant, as well as propranolol (20 mg every 6 h), ranitidine (150 mg bid), prednisone (10 mg every day), nifedipine XL (60 mg every day), and aspirin, all given orally. The preoperative blood urea nitrogen was 29 mg% and the creatinine was 1.8 mg%. Upon arrival in the operating room, standard monitoring was begun which included radial artery and pulmonary artery catheters. An anesthetic consisting of sufentanil (15 μg/kg), vecuronium (20 mg), and midazolam (5 mg) was administered intravenously.

The operation proceeded with the placement of three saphenous venous grafts and one left internal mammary graft. The aortic cross-clamp time was 70 min, and the total cardiopulmonary bypass time was 160 min. Separation from cardiopulmonary bypass was facilitated with intravenous infusions of nitroglycerine (50 μg/min) and dobutamine (5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The remainder of the procedure was uneventful.

The cardiopulmonary bypass circuit was composed of an M2000 Shiley membrane oxygenator with polyvinylchloride circuit tubing (Baxter Laboratories). The pump prime consisted of 500 mL of 20% mannitol, 500 mL of 5% albumin, 100 mL of 25% albumin, 100 mEq of $NaHCO_3$, 10,000 U of heparin, and 1000 mL of Plasmalyte. No hemoconcentrator was used.

Plasma CsA levels at 3, 2, and 1 day before surgery, while receiving an oral CsA dose of 400 mg daily, were 54, 109, and 42 ng/mL, respectively. The preoperative hematocrit was 38%. On the day before surgery, CsA (100 mg IV × 2) was given with a 12-h interval between doses. The second intravenous CsA dose was administered 4 h before surgery.

In the operating room, CsA samples were drawn at 2 h and at 30 min prebypass with a core temperature of 36°C and a hematocrit of 36.5%. Cyclosporin A samples were drawn at 3, 30, and 60 min while on bypass, with corresponding patient temperatures of 36, 28, and 28°C and hematocrit levels of 28%, 24%, and 22%, respectively. Postbypass CsA samples were drawn at 3 and 60 min with a core temperature of 37°C. A hematocrit of 23% was obtained immediately after bypass and the patient received 2 U of packed red blood cells in the operating room. A hematocrit of 34% was obtained 3 h postoperatively.

Cyclosporin A therapy was reinstituted 2 h postoperatively as 100 mg IV, every 12 h for 3 days. This was changed to an oral dose of 400 mg daily on the fourth postoperative day. Plasma CsA levels drawn on the fourth, fifth, and sixth postoperative days were 201, 20, and 27 ng/mL, respectively.

Each CsA sample consisted of 3 mL taken from the radial artery catheter and was immediately refrigerated at 4°C before assay. Eight hours after the last intraoperative sample was drawn, all of the samples were immersed in a water bath at 37°C for 30 min, centrifuged at 37°C, and the plasma assayed. The

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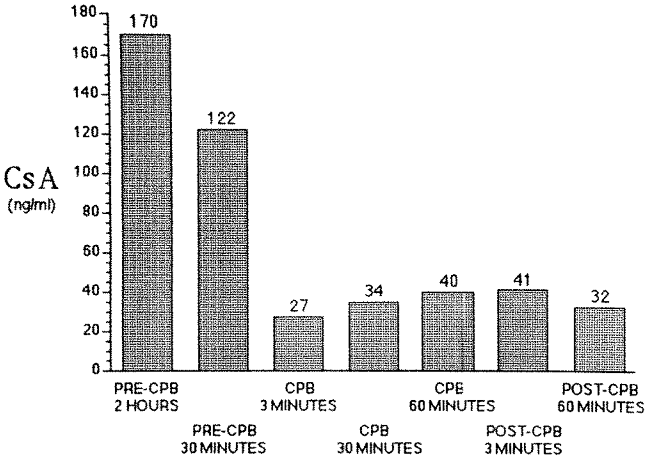

Figure 1. Correlation between blood concentration of cyclosporin A (CsA) and various times during the pericardiopulmonary bypass (CPB) period.

determination of free CsA plasma levels at our institution utilizes a radioimmunoassay of a specific monoclonal antibody (The Sandoz Sandimmune Kit, INCSTAR Corporation, Stillwater, Minn.). The therapeutic range of CsA in plasma is considered to be 150–250 ng/mL (12), with the accuracy of this kit stated as a coefficient of variation of 5% at 23 ng/mL and 2.4% at 229 ng/mL.

Discussion

Monitoring of serial CsA levels is probably important in the management of posttransplant patients to assure adequate drug dosage and to minimize toxicity (6), particularly the nephrotoxicity associated with higher levels. Cyclosporin A is a hydrophobic cyclic peptide composed of 11 amino acids (6). It has a variable absorption after oral administration (10%–70%) and takes from 1 to 3 h to develop peak blood concentrations. It is highly protein-bound with from 50% to 60% contained within erythrocytes, and its excretion is predominantly via hepatic metabolism. Less than 6% is excreted unchanged in the urine, and the elimination half-life is approximately 12 h (13).

The multiple determinations of CsA levels in this patient demonstrated that drug levels fell quickly and substantially with the beginning of cardiopulmonary bypass and remained subtherapeutic 1 h after discontinuation from bypass (Figure 1).

Other categories of drugs have demonstrated significant blood concentration changes during and after cardiopulmonary bypass. Propranolol levels decrease markedly after initiation of cardiopulmonary bypass and rebound to approximately half of the prebypass levels upon discontinuation of bypass (9). Hemodilution was cited as the major factor in this effect with contributions of altered protein binding and a changed volume of distribution. Cefazolin levels decrease with initiation of bypass and, after discontinuation of bypass, rebound to levels higher than prebypass (11). Pancuronium infusion requirements necessary to maintain a specific degree of neuromuscular blockade increase above control levels with the beginning of bypass, decrease during bypass, and increase above control during rewarming (10).

Numerous factors can significantly alter the normal pharmacokinetics of a drug during cardiopulmonary bypass. These include dilution of red blood cells and plasma proteins from the pump priming volume, altered hepatic or renal excretion secondary to changes in organ perfusion and hypothermia, and binding to the membrane oxygenator or bypass circuit material.

The large and rapid decrease of CsA levels detected immediately on initiation of bypass was most likely due to the hemodilution from the pump prime volume, with corresponding measured hematocrits decreasing from 38% to 28% and eventually to 22%. Other factors, however, may contribute to a decrease of CsA levels. CsA binds significantly to an intraerythrocyte protein. The transfusion of red blood cells perioperatively would theoretically decrease CsA levels as unbound drug equilibrates with new red cells. Additionally, a shift of CsA into erythrocytes with decreasing temperatures has been described (14). Finally, binding to parts of the membrane oxygenator or pump tubing cannot be excluded.

Many studies have commented on the marked degree of individual variability of oral absorption, metabolism, and steady-state CsA levels in nonsurgical patients, but none have addressed the perioperative period (if there are changes in CsA levels and if these correlate with organ survival).

Our patient received his renal transplant more than 5 yr previously, and as the necessity to adhere strictly to a particular CsA level appears to be dependent on the time elapsed since transplantation (15), the considerations of a decrease in CsA levels during and after cardiopulmonary bypass are most likely not clinically significant in this case. However, although we present results of one patient only, we suggest that, for patients who have received a recent renal transplant and require cardiac surgery and who are in a period where a marked decrease in CsA levels could adversely affect organ survival, a CsA determination be done early after cardiopulmonary bypass to facilitate the reestablishment of therapeutic levels.

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Unilateral Bronchospasm After Interpleural Analgesia

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The interpleural block (IPB) is used for a variety of surgical procedures, postsurgical pain, and other painful conditions (1–11). Common complications resulting from IPB analgesia are Horner's syndrome, phrenic nerve paralysis, and pneumothorax (2–11). A case of unilateral bronchospasm after IPB is presented.

Case Report

A 38-yr-old nonasthmatic female patient with a tennis ball-sized hepatoma on the right lobe was treated by injecting alcohol into the tumor mass. The first injection of alcohol under local anesthetic was extremely painful; therefore, subsequent procedures were performed using IPB with the patient in the left lateral decubitus position. The interpleural catheter was introduced at the T-7 intercostal space, 6 cm lateral to the midline. The patient was turned on her back with a 10° reverse Trendelenburg position. Thirty milliliters of bupivacaine (0.25%) with 1:200,000 epinephrine was slowly injected through the catheter. A second dose of 15 mL was given 30 min after the first injection. The patient had analgesia from the T-4 to the T-12 area on the right side with stable vital signs. Under radiographic monitoring, 100 mL of alcohol was injected into the tumor and the interpleural catheter was removed without pain. Fluoroscopy showed elevated right hemidiaphragm with no pneumothorax.

While in the postanesthesia care unit, approximately 30 min after the procedure (90 min after the injection of local anesthetic), the patient became anxious, expressed difficulty in breathing, and was tachypneic with respiratory rate of 32 breaths/min. Although the patient was receiving nasal oxygen, oxygen saturation decreased from 97% to 92%. Auscultation of the chest showed severe inspiratory and expiratory wheezing and rhonchi throughout the right lung. The left lung had normal breath sounds. The chest radiograph showed no pneumothorax.

The patient was monitored for 2 h without administration of bronchodilators. The right-lung bronchospasm gradually disappeared with sensory and motor recovery. Oxygen saturation returned to 97%, and the patient experienced no more difficulty in breathing.

Discussion

The IPB is usually a safe procedure and provides good analgesia. The danger of pneumothorax is rare in experienced hands (5,6). In a series of more than 30 IPBs, there has been no incidence of pneumothorax (9–11). Accidental lung damage by introducer needle or by intrapulmonary placement of interpleural catheter in patients with pleural thickening (fibrosis) or with any condition associated with lungs adhering to the chest wall is also possible. Complications such as hemothorax, pleural effusion, infection, pleural shock, cardiac and central nervous system toxicity, and allergic reaction should also be kept in mind. Horner's syndrome and phrenic nerve paralysis are not uncommon (2–4,7–11).

There are many reports of bronchospasm after interscalene brachial plexus blocks (12–14), spinal and general anesthesia (15,16), intercostal phenol nerve blocks (17), kidney transplantation (18), and prostaglandin injection used to stop uterine bleeding under general anesthesia (19). There are no reports of unilateral or bilateral bronchospasm after IPB. Understanding the nerve supply to the lungs, their relation to the parietal pleural reflection, and the role of various bronchodilators, constrictors, receptors, and mediators may shed light on the possible mechanism of this rare complication. Vagal and sympathetic fibers in the anterior and posterior pulmonary nerve plexuses around the hilum supply the tracheobronchial tree and the lungs. The vagal branches contain preganglionic parasympathetic bronchoconstrictor efferent fibers from dorsal vagal nucleus and visceral sensory afferent fibers from inferior vagal (nodose)

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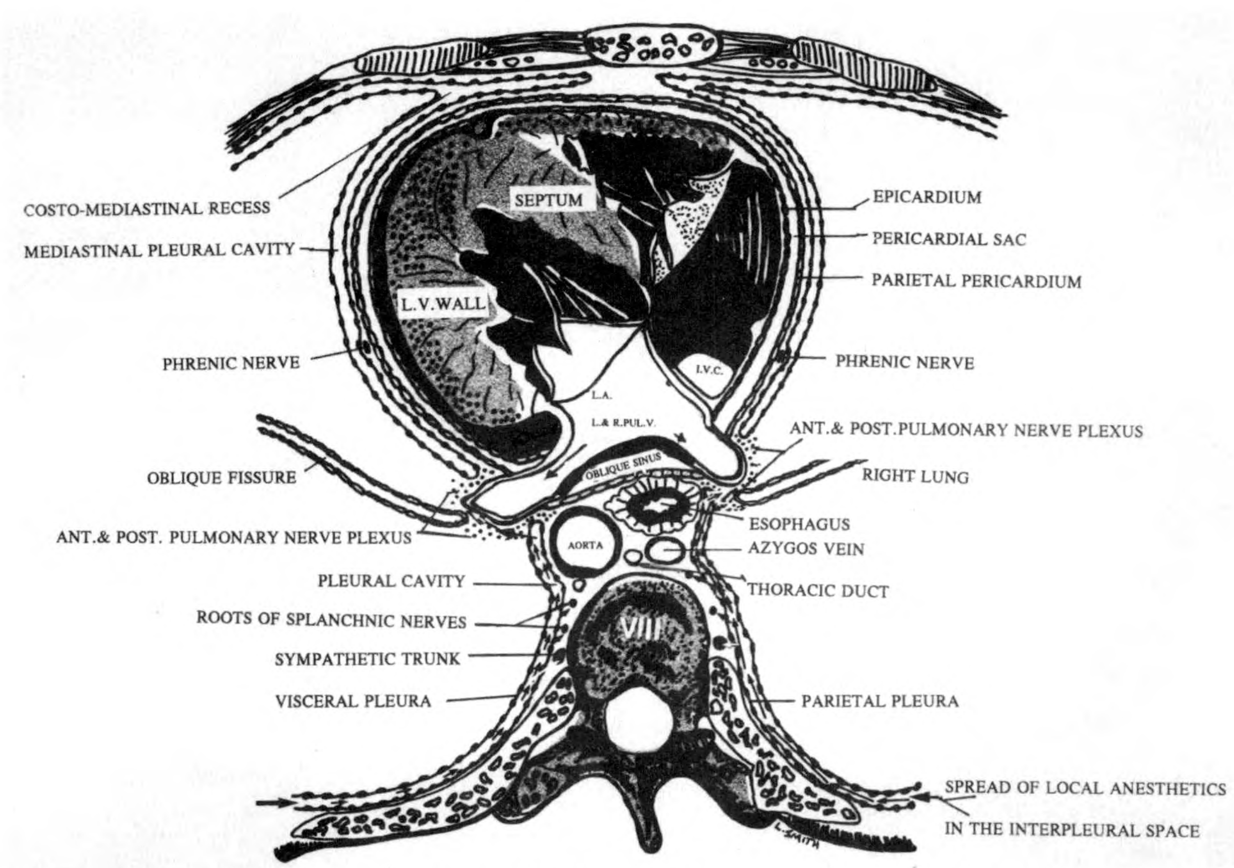

Figure 1. Cross section of the thoracic cavity showing the interpleural space, hilum of the lungs, pericardial sac, and various nerve structures related to the pleural and pericardial cavity. The sympathetic chain, its postganglionic fibers, and the anterior and the posterior pulmonary plexuses are closely related to the parietal pleura and the paravertebral and mediastinal pleural cavities. The local anesthetics in the pleural cavity (*arrows*) can be easily conducted through the parietal pleura and block the sympathetic nerve fibers at various locations (*arrows*), contributing to bronchospasm.

ganglia. Sympathetic fibers contain postganglionic bronchodilators and visceral afferent fibers arising from T2-5 segments (sometimes T-1, T-6, and T-7). The mediastinal pleural cavity meets at the hilum of the lung and pulmonary ligament and comes in direct contact with the pulmonary plexuses (Figure 1).

Any technique that interrupts the sympathetic outflow sparing the parasympathetic outflow to the lungs can initiate or aggravate an asthmatic attack (20).

1. Unilateral bronchospasm could be due to (a) blockade of the sympathetic supply to the lung by blocking the sympathetic chain and its ganglion supplying the lungs (Figure 1); (b) blockade of the postganglionic fibers from the sympathetic ganglion to the pulmonary plexus; and (c) gradual migration of local anesthetic to the mediastinal pleural cavity around the hilum and the pulmonary ligament and blockade of the pulmonary plexus (Figure 1, arrows). The posterior pulmonary plexus, rich in sympathetic fibers, is more accessible for local anesthetic spread from the paravertebral space (Figure 1).
2. Stimulation of the superficial airway receptors (mediated by vagus) in the tracheobronchial tree by a divergent group of stimuli such as inhalation of cold air (20), sulfur dioxide gas (21), or chemically inert dust (22), rapid respiratory movements (23), and emotional and psychological factors (24) can result in bronchospasm. These processes can be abolished in animals by cutting the vagus (25) or by administration of atropine (26) or can be induced by neostigmine, acetylcholine, histamine, and serotonin (13). The water droplets from the humidifier, cold oxygen from the wall supply, and rapid breathing due to diaphragmatic paralysis could stimulate the receptors supplied by the vagal fibers; and the associated sympathetic blockade by IPB probably facilitated the development of bronchospasm (20).
3. There is a possibility of bronchospasm initiated by necrosed tumor tissue, local anesthetics, histamine, serotonin and acetylcholine release after the block, and injected alcohol permeating through the liver and the diaphragm. Unilateral bronchospasm rules out any such possibility.

4. Existence of direct sympathetic nerve supply to the bronchial smooth muscle is questionable (27,28). However, the histochemical fluorescent technique has shown an extensive network of catecholamine-containing nerves throughout the tracheobronchial tree (29). It is not understood how these nerves exert their influence on the bronchial smooth muscles, whether through the circulating catecholamines or directly (30). The sympathetics to the adrenal gland is derived from T10-L1. The epinephrine output from the right-side adrenal gland may have been reduced owing to splanchnic sympathetics blockade. A decrease in circulating epinephrine (31), associated with blockade of the sympathetic supply to the lungs and with stimulation of airway receptors, could have resulted in unilateral bronchospasm.

The integrity of normal airway is a balance between β-adrenergic bronchodilatation and the vagal parasympathetic and α-sympathetic bronchial constriction. Unilateral bronchospasm can be missed owing to its delayed onset and paucity of symptoms. The administration of atropine and other vagolytic agents may be considered before IPB. Simultaneous bilateral IPB may be avoided in patients with severe chronic obstructive pulmonary disease and asthma and in those on β-adrenergic blockers. An IPB in these patients could result in bilateral diaphragmatic paralysis, with added bronchospasm precipitating a respiratory emergency.

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Bilateral Analgesia and Unilateral Paresis After Lumbar Epidural Blockade

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One of the most intriguing causes of unilateral epidural blockade is the presence of a connective tissue band that binds dura mater and flaval ligament at the dorsal midline ("plica mediana dorsalis") and divides the epidural space into a ventral and two dorsolateral compartments (1–8). We have observed, and here describe, a bilateral analgesia associated with right unilateral motor and sympathetic block after lumbar epidural anesthesia. An epidurographic examination at the end of the operation showed a unilateral distribution of the dye, which was confined to the right side of the lumbar space. Formerly in the same patient, an attempt of lumbar epidural blockade resulted in a right unilateral sensory and motor block.

Case Report

A 37-yr-old woman weighing 69 kg required anal sphincteroplasty as she suffered from incontinence after a fistulectomy performed 3 mo earlier. She was healthy and there was neither history of previous surgery of the lumbar spinal area nor history of meningitis. The only remarkable medical event was a unsuccessful epidural anesthesia for the ligature of the left leg saphenous vein. Epidural blockade was performed with a 17-gauge Tuohy needle inserted in the midline, with the patient in the sitting position. Administration of 12 mL of 0.50% bupivacaine with epinephrine 1:200,000 resulted in a right-sided sensory and motor block. Thus, the surgical procedure was carried out under general anesthesia.

Shortly before the anesthetic procedure, 0.5 mg of atropine and 5 mg of morphine were given intramuscularly as premedication. The patient was taken to the operating room. An intravenous infusion was started, and monitoring devices were applied. Continuous lumbar epidural blockade was chosen in view of the probable duration of the proposed surgical procedure. With the patient in the sitting position, a midline approach was used and a 17-gauge Tuohy needle was inserted at the third lumbar vertebral interspace. The epidural space was easily identified at 3 cm from the skin by the loss of resistance to air technique. Ten minutes after a 3-mL test dose of 0.50% bupivacaine with epinephrine 1:200,000, a 12-mL bolus dose of the same local anesthetic solution was injected. A 0.9-mm catheter was then inserted 2 cm in a cephalad direction, and an additional 5 mL of 0.50% bupivacaine with epinephrine was administered through the catheter. After the needle was removed, the patient was placed in the supine position. A complete bilateral loss of pinprick sensation developed up to the T-10 dermatome in approximately 15 min. On the contrary, the patient complained of weakness only in the right leg, and objective motor block, according to Bromage's scale (9), was totally absent in the left leg. Moreover, the skin of the right foot appeared warmer than that of the left foot, and the patient herself referred to a subjective feeling of warmth in the right limb. Unfortunately it was not possible to perform any specific test to assess the degree and extent of the sympathetic block.

During the 95 min of uneventful surgical procedure, no further injection was made. At the end of the operation, after informed consent was obtained from the patient, 8 mL of iopamidol (200 mg/mL) was injected through the epidural catheter, and an epidurography was taken. The anteroposterior view of the spine showed a unilateral distribution of the dye, which was confined exclusively to the right side of the lumbar epidural space (Figure 1). The patient was then placed in the left lateral position for 5 min, but no change was observed after this as the dye did not fill the left side of the epidural space. At this time unilateral paresis and sympathetic block, together with radiologic imaging, strongly suggested the presence of the plica mediana dorsalis. In addition, this midline tissue membrane barrier explained the right-

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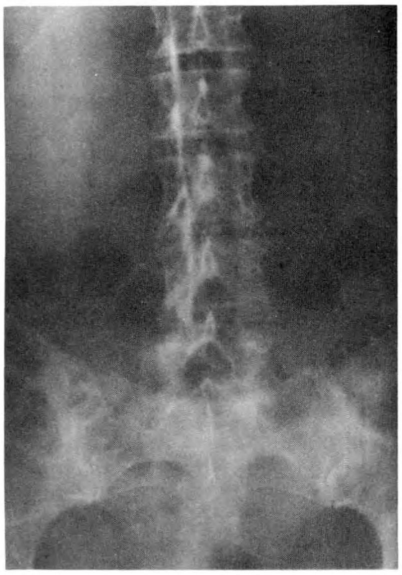

Figure 1. Epidurography (anteroposterior view) obtained after administration of 8 mL of iopamidol through the epidural catheter. Contrast medium has spread exclusively to the right side of the lumbar epidural space. The epidural catheter is not evident owing to its lack of radiopacity. In addition, after the contrast medium had been injected, the catheter was washed with saline to avoid possible occlusion.

sided sensory and motor block after the previous lumbar epidural anesthesia and that here described, but this was apparently incompatible with the present, well-checked bilateral analgesia.

Intramuscular morphine provided suitable analgesia for the postoperative period. The patient was discharged on the sixth postoperative day without complication.

Discussion

The occurrence of unilateral sensory and motor block during epidural anesthesia is rather common (6,7,10–14) but bilateral analgesia combined with unilateral paresis and sympathetic block is not. In the case described, the epidurographic evidence of right unilateral spread of the contrast medium accounts for the right sensory, motor, and sympathetic block. However, it does not explain the development of a left-sided sensory block. We may hypothesize that the local anesthetic solution might have diffused within the spinal white matter, reaching by this way the sensory fibers coming from the left side. In fact, the great majority of the sensory fibers that enter the spinal cord via the dorsal horn decussate before ascending to the brain, running somewhat on the surface of the anterolateral white matter (15). Both the injection of the whole volume of bupivacaine (20 mL) into the right dorsolateral compartment and the impossibility of contralateral dispersion might have facilitated spinal uptake. Spinal cord effects of epidural blockade have been proposed by Bromage (16) following his observations of changes in lower limb reflexes associated with thoracic epidural blockade. This is also supported by autoradiographic studies: a specific uptake of radioactively labeled epidural local anesthetics by the neuraxis (17) in concentrations sufficient to block nerve conduction (18,19) has been observed.

Cohen (19) found substantial differences in the concentration of intrathecally administered local anesthetic in different parts of the spinal cord of the dog, with about twice as much drug present in the dorsal and lateral columns as compared with that found in the anterior columns. Thus, it seems reasonable to assume that, in turn, the observed unilateral sympathetic block could have also been caused to some extent by diffusion of the local anesthetic within the peripheral part of the spinal dorsolateral columns. Indeed, the descending excitatory sympathetic fibers run somewhat on the surface of the dorsolateral funiculus.

Because the axons of the corticospinal tract run somewhat deeply in the lumbar spinal cord, it is quite unlikely that unilateral paresis could have been caused by diffusion of the local anesthetic within the anterior columns.

One can object that the spread of radiopaque dye does not necessarily mirror that of a local anesthetic solution, so a small volume of the injected bupivacaine might have escaped to the left dorsolateral compartment leading to ipsilateral analgesia. Nevertheless, in that case an incomplete or "patchy" epidural block would have developed instead of a loss of pinprick sensation from the T-10 to the S-5 dermatome.

The history of a previous right unilateral sensory and motor block, together with radiologic imaging of wide extension and completeness of the median fold, strongly suggests a congenital rather than acquired genesis of the midline adhesions. We believe that the unilateral analgesia and paresis after the first lumbar epidural anesthesia could be due to the deviation of the Tuohy needle tip to the right side of the epidural space. Nevertheless, one could ask why in that circumstance a contralateral sensory block did not develop? As only 12 mL of 0.50% bupivacaine with epinephrine was injected, we may hypothesize that this dose is inadequate to produce intraspinal sensory block. Also, in some reported cases of hemianalgesia caused by congenital or acquired midline adhesions, the injected dose of local anesthetics was probably insufficient for intraspinal block of contralateral sensory fibers. However, we cannot deny that our patient may have some anatomic peculiarity.

In summary, we present a case of bilateral analgesia and unilateral motor and sympathetic block after lumbar epidural anesthesia in which the presence of a dorsal midline band was confirmed radiologically. Formerly, the same patient had undergone lumbar epidural blockade, and a unilateral analgesia and paresis had developed. Discussion involves the possible mechanisms by which these findings might have taken place.

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Management of Epidural Anesthesia in a Patient With Takayasu's Disease

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Takayasu's disease is a chronic inflammatory arteriopathy of uncertain origin (1). It results in progressive obliteration of the lumina of the aorta, its branches, and/or the pulmonary artery. Several authors have cautioned against the use of regional anesthesia in Takayasu's disease because of the dangers of hypotension and subsequent vasopressor use (2,3), or they have failed to detail its use in the obstetric patient (4,5). Yet severe life-threatening complications of Takayasu's disease (e.g., exacerbation of hypertension, cardiac failure, or cerebral hemorrhage) may occur during labor and delivery (5) and may perhaps be best avoided through the use of epidural blockade. We present a severe case of Takayasu's disease during pregnancy with successful delivery and postpartum tubal ligation with epidural anesthesia.

Case Report

A 20-yr-old gravida 2, para 1, Hispanic woman with Takayasu's disease was admitted at 40-wk gestation for elective induction of labor to be followed by postpartum tubal ligation. She had previously undergone an uneventful delivery at age 16 yr, but 2 yr later, she suffered a left-sided cerebrovascular accident with resultant right hemiplegia and an expressive aphasia.

A full cardiovascular evaluation was conducted. Echocardiogram revealed trace tricuspid, mitral, and aortic insufficiency with a 49% ejection fraction. Carotid Doppler studies showed no blood flow in the right carotid artery and severe flow limitation in the left artery. These findings were verified by an arch arteriogram that demonstrated total right carotid artery occlusion, subtotal left carotid artery occlusion, and total right brachiocephalic artery occlusion. A chest radiogram was unremarkable.

Physical examination on admission revealed the following: blood pressure, 85/60 mm Hg in the left arm and 140/80 mm Hg in the left thigh; heart rate, 86 beats/min with an absent right carotid pulse, a 1+/4+ left carotid pulse with a 2+/4+ bruit, an absent right radial pulse, a 1+/4+ left radial pulse, 2+/4+ femoral pulses bilaterally, and 1+/4+ dorsalis pedis pulses bilaterally. Fundi were benign; respirations were 19 breaths/min; the lungs were clear by auscultation; heart sounds were regular with a 2+/4+ systolic ejection murmur at the lower left sternal border; and the extremities showed no edema but were remarkable for well-healed severe burns on the left leg (a result of spilled grease during late pregnancy and yet a cause of virtually no distress to the patient at the time of the accident).

The patient was alert and cooperative, appeared to understand her condition (via interpreter), but had a very flat affect. In addition to poor sensory function, she had no motor strength, exaggerated reflexes, clonus, and a positive Babinski sign on her right side. Left-sided findings were normal. Pelvic examination revealed cervical dilation of 2 cm and a vertex presentation with occiput posterior.

A peripheral intravenous infusion was begun followed by placement of a right subclavian venous catheter and a right femoral arterial catheter. Initial central venous pressure was 5 mm Hg. Femoral arterial pressure was 180/95 mm Hg. Other monitoring included a continuous electrocardiogram and pulse oximetry. Following the intravenous administration of lactated Ringer's solution (1000 mL), lumbar epidural anesthesia was initiated using 0.25% bupivacaine with 5 μg/mL of fentanyl. Over the initial 10 min, 6 mL of solution was injected through the epidural needle followed by an additional 4 mL over 10 min through the catheter, resulting in a T-10 sensory level. Anesthesia was maintained with an 8-mL/h infusion of 0.125% bupivacaine with 1 μg/mL of fentanyl. Amniotomy to allow direct fetal heart rate monitoring was performed with the patient nearly supine. A decrease in arterial blood pressure to 120/60 mm Hg occurred after amniotomy. Resump-

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tion of the lateral position did not restore baseline arterial blood pressure. Therefore, 500 mL of lactated Ringer's solution, and 10 mg of ephedrine (in 5-mg doses) were given intravenously to maintain systolic pressure near baseline at >160 mm Hg. Oxytocin was used to induce labor. During the subsequent 8.5 h, labor progressed normally, sensory levels of T-4 were maintained, and blood pressure remained between 160/80 and 200/100 mm Hg. Central venous pressure ranged from 4 to 9 mm Hg. Oxygen saturation, measured in the left index finger, was 94%–96%. Fetal heart rate was 130–160 beats/min with normal short- and long-term variability.

Intense analgesia resulting from 16 mL of 0.5% bupivacaine given incrementally over 30 min facilitated the use of low-outlet forceps to avoid maternal straining during stage 2. A healthy, 3422-g female infant was delivered. Postpartum tubal ligation was performed without further anesthetic requirement. Arterial blood pressure, heart rate, electrocardiogram, and central venous pressure remained stable. Blood loss was 450 mL. The patient had an uneventful recovery with discharge from the hospital 2 days after delivery. She declined follow-up care.

Discussion

Takayasu's disease (pulseless disease) is a nonspecific obstructive arteritis with a predilection for the aortic arch that occurs most frequently in Asian and Hispanic women in the second and third decade of life (4,6). It may be the result of an autoimmune phenomenon (7), but this is by no means certain. It is progressive and frequently fatal (4). Signs and symptoms include vertigo, visual disturbances, syncope, seizures, stroke, carotid and coronary artery disease, cardiac valvular and conduction disease, peripheral artery occlusion, pulmonary hypertension, and renal artery stenosis (8).

Classification of Takayasu's disease is dependent on the distribution of lesions (7,9). Type I affects the aortic arch and/or its branches. Type II affects the thoracic and abdominal aorta without involvement of the arch. Type III is a mixture of type I and type II. Type IV includes pulmonary artery involvement. Our patient did not manifest pulmonary disease but did have known disease of the aortic arch (type I).

Pregnancy in Takayasu's disease may be associated with worsening hypertension, congestive heart failure, and possible cerebral hemorrhage (2,5). The hypercoagulable state induced by pregnancy is especially dangerous in patients like ours with significant arterial lesions (3).

Epidural analgesia was chosen to provide effective pain control and cardiovascular stability. Vaginal delivery with low-outlet forceps likewise avoided the more marked impact on the cardiovascular system that may have resulted from either cesarean section or repeated Valsalva maneuvers associated with the second stage of labor (2,5). Accurate arterial blood pressure measurement required an arterial line to be placed in a large artery. Because of this patient's significant carotid disease, preinduction levels of arterial blood pressure were maintained to avoid possible cerebral ischemia. At the same time, further increases from this hypertensive baseline state were avoided to prevent undue cardiac strain and hemorrhagic stroke (5). The use of epidural anesthesia prevented labor-induced exacerbation of hypertension, precluding the need for antihypertensive drug therapy.

Avoidance of block-induced hypotension is important in Takayasu's disease because of the possibility of regional and especially cerebral hypoperfusion (3,5). Uterine displacement is mandatory. At least 15 mL/kg of crystalloid should be given before initiation of epidural blockade. Finally, the administration of local anesthetic should be very slow, allowing time to adjust for the development of sympathetic block. A decrease in arterial blood pressure may then be managed with further intravenous fluid administration or judicious doses of ephedrine. Although use of a flow-directed pulmonary artery catheter has been recommended (4), the essentially normal echocardiogram with a good ejection fraction made us confident that CVP measurements would provide adequate information about cardiac preload in this patient.

While this patient had a relatively high level of sensory blockade (T-4) during the latter stages of labor, this resulted from a rather minimal infusion of anesthetic (0.125% bupivacaine at 8 mL/h). Although a decrease in the infusion rate would likely have decreased the extent of blockade, our patient was very stable from a hemodynamic standpoint and had minimal motor blockade. Thus, a decrease in the infusion rate, which may have led to the loss of adequate analgesia, was deemed unnecessary. The incremental addition of 16 mL of 0.5% bupivacaine to facilitate the use of forceps and subsequent tubal ligation did not appreciably increase the extent of sensory blockade.

Pulse oximetry was easily obtained in this patient despite poor peripheral pulses. As oximetric monitoring began after sympathetic blockade, the latter may have improved peripheral perfusion and facilitated the oximetric measurements.

In conclusion, we describe the successful use of epidural analgesia for labor, delivery, and tubal ligation in a patient with Takayasu's disease. Consistent with previous reports (10,11), we placed prime importance on maintenance of normal central venous pressure (preload) and arterial blood pressure during sympathetic blockade resulting from epidural anesthesia.

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A Retained Esophageal Stethoscope as a Potential Cause of Small Bowel Obstruction

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A variety of complications have been described after the use of esophageal stethoscopes, including hypoxia secondary to tracheal or endobronchial misplacement (1–3), surgical errors secondary to misidentification of anatomic structures (4,5), and hypoxia related to reduction in pulmonary blood flow by compression of an aortopulmonary collateral in an infant with complex cyanotic congenital heart disease (6). We describe the unrecognized retention of an esophageal stethoscope, for which the patient presented 6 mo later with clinical evidence of a partial small bowel obstruction.

Case Report

A 74-yr-old man was scheduled for a right colectomy and wedge biopsy of a liver mass in July 1990. His past medical history was significant for stable coronary artery disease and mild aortic stenosis. He was admitted with dyspnea on minimal exertion in February 1990. Evaluation at that time revealed mild anemia and a cardiac murmur. Subsequent echocardiogram revealed an ejection fraction of 62% and mild aortic stenosis, with a peak systolic gradient of 34 mm Hg and aortic valve area of 1.3 cm^2. An exercise stress test was performed and revealed ST segment depression accompanied by chest discomfort. A medical regimen of atenolol (50 mg daily), diltiazem (30 mg qid), and isosorbide dinitrate (10 mg qid) was started, and repeat dipyridamole-thallium scan revealed no angina, nonspecific electrocardiographic changes, and normal thallium images with no redistribution, fixed defects, or delayed lung uptake. Colonoscopy was performed and biopsy revealed adenocarcinoma.

Preoperative laboratory values were significant for the following: hematocrit 32%, blood urea nitrogen 17 mg/dL, creatinine 1.2 mg/dL, and electrocardiographic sinus rhythm with nonspecific ST and T wave changes. The patient received an uneventful combined epidural and general anesthetic. A lumbar epidural catheter was inserted at L3-4 without difficulty, and epidural anesthesia was induced with 2% lidocaine with epinephrine (200 mg), achieving a T-6 level. General anesthesia was then induced with thiopental (300 mg IV), followed by 1500 μg of alfentanil. Muscle relaxation was provided by vecuronium. The trachea was intubated with an 8.0 Mallinckrodt oral endotracheal tube, and ventilation was controlled. An esophageal stethoscope was inserted, and subsequent anesthesia was provided by 70% nitrous oxide, 0.25%–0.5% isoflurane, in addition to 0.5% epidural bupivacaine, and an epidural infusion of 0.125% bupivacaine/100% fentanyl at 5 mL/h. Intraoperatively, the surgical staff requested that a nasogastric tube be inserted. An 18F nasogastric tube was inserted into the stomach through the right nares, and its position in the stomach was confirmed by the surgeons. An uneventful right colectomy and wedge biopsy of the liver was performed. Neuromuscular blockade was reversed with intravenous neostigmine and glycopyrrolate, and the trachea was extubated uneventfully.

The patient spent 24 h in the postanesthesia care unit to receive the benefits of epidural narcotic analgesia and was transferred to the floor. He was discharged on the ninth postoperative day. Pathologic examination revealed adenocarcinoma of the colon with metastases to the liver.

Follow-up computed tomography scan of the abdomen performed in December 1990 revealed multiple liver metastases, bilateral adrenal metastases, a partial right hydroureter, and recurrent disease in the surgical bed. Oncology service consultation was obtained, and the patient was scheduled for chemotherapy to begin in January 1991.

He was admitted to the emergency department on January 4, 1991, complaining of anorexia and nausea for 3 days and vomiting for 24 h. He denied symptoms or signs of gastrointestinal bleeding, and his

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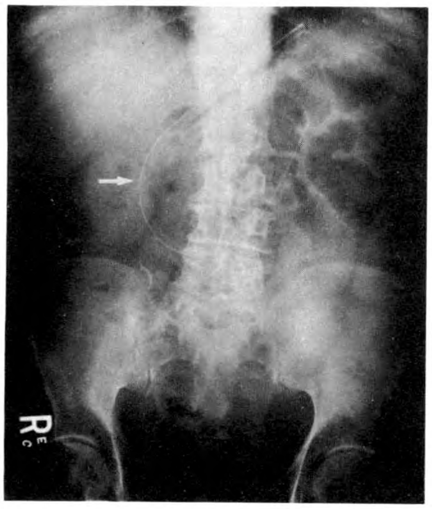

Figure 1. Abdominal radiograph revealing the coiled esophageal stethoscope in the stomach.

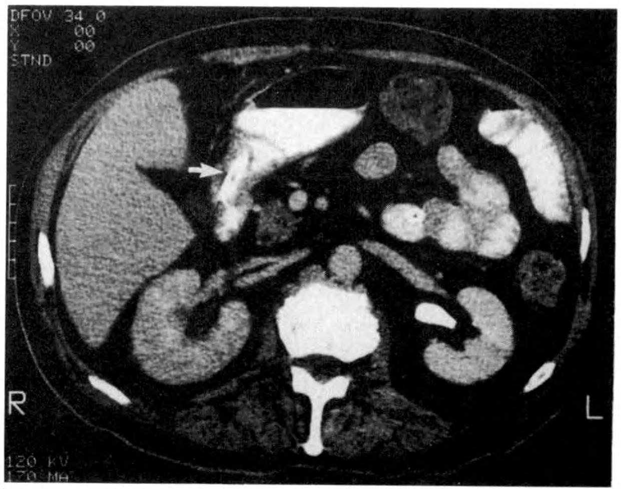

Figure 2. Abdominal computed tomography scans revealing the esophageal stethoscope in the stomach and exiting into the duodenum.

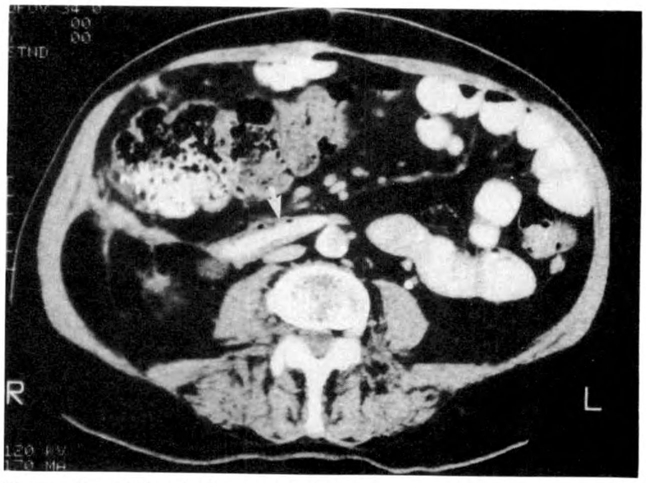

Figure 3. Abdominal computed tomography scans revealing the esophageal stethoscope in the stomach and exiting into the duodenum.

physical examination was significant for mild but diffuse tenderness without peritoneal signs. A plain radiograph of the abdomen was obtained (Figure 1) that revealed a radiopaque tube coiled in the stomach, extending into the first part of the duodenum. In addition, several air-fluid levels were noted, consistent with a partial small bowel obstruction. An esophagogastroduodenoscopy was performed on the next day, and snare removal of an 18F esophageal stethoscope (Sheridan Sonascope) was performed without complication. On removal, the stethoscope was noted to be very stiff; however, it had not caused any mucosal ulceration or perforation. Nasogastric tube decompression was performed and the bowel obstruction was relieved after 2 days. In retrospect, the retained esophageal stethoscope was visible on his abdominal computed tomography scan in December 1990 (Figures 2 and 3).

Discussion

A search of the literature reveals this case to be the first report of accidental retention of an esophageal stethoscope of such duration. Though the patient had several other factors that may have contributed to the development of his small bowel obstruction (e.g., adhesions from prior surgery and recurrent metastatic disease), the esophageal stethoscope likely influenced bowel function, particularly because it was so stiff. Kugler et al. (7) have also reported marked stiffness of an esophageal stethoscope accidentally retained for 4.5 wk. Lack of mucosal damage was also noted in a report by Hoffman and Jedeikin (8) of an accidentally retained endotracheal tube present in a patient's stomach for 9.5 mo before removal by laparotomy.

We also have had four other cases of partially retained esophageal stethoscopes in the past 2 yr. These were noted in patients either in the operating room or in the postanesthesia care unit after active retching, gagging, and coughing during or following emergence from anesthesia. We have discussed this case with the manufacturer and have suggested the utility of adding some sort of retention device to remind practitioners of its presence (Figure 4).

It is our assumption that the esophageal stethoscope (which was placed early during the anesthetic) passed further into the esophagus from frictional contact during insertion of the nasogastric tube. The occurrence of this complication was a function of

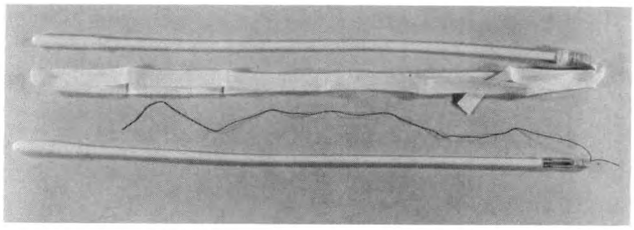

Figure 4. Potential modifications of the esophageal stethoscope with retention suture or tape applied.

focusing on the myriad tasks involved after anesthetic induction, and the interruption of constant monitoring via the esophageal stethoscope to perform them. This particular device is 40 cm in length, and in an average adult, breath sounds will be audible when the end of the esophageal stethoscope is placed 12–40 cm from the teeth, and heart tones will be audible when the end is positioned 19–40 cm from the teeth. Thus, in general, such monitors should protrude from the mouth 10–15 cm when in use.

An esophageal stethoscope is a useful monitor of core temperature during hypothermic cardiopulmonary bypass, provides information regarding bronchospasm, and may be a back-up system for the detection of ventilator disconnection, accidental extubation, and kinked endotracheal tubes (9).

In summary, we present the case of an accidentally retained esophageal stethoscope that may have contributed to a patient's bowel obstruction 6 mo later. We suggest that increased vigilance, as well as taping in place all monitoring devices or placing a retention device on them, should prevent future cases such as ours.

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Guide-Wire Retention After Right Atrial Catheter Insertion

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The use of a right atrial catheter for sitting position cases at risk for venous air embolism is a common clinical practice (1). The risks are generally believed to be minimal, especially when the catheters are inserted from the arm. This case describes a complication of which we were not previously aware.

Case Report

The patient is a 43-yr-old woman who presented with foot drop for possible lumbar laminectomy. The only pertinent medical history was a cervical laminectomy at our hospital 2 yr before this admission. The radiologist identified a "central line" in place on a chest radiograph. The patient had no signs or symptoms related to this finding. On close examination of the films, the central device was believed to be a wire without a "J" on the distal end (in the superior vena cava [SVC]) with the proximal end at the antecubital fossa. The wire coursed through the right cephalic vein laterally. Echocardiography demonstrated no thrombus adherent to the wire and venogram showed a patent system from arm to the SVC. Review of the previous anesthesia record showed the use of an Arrow Kit No. 04250 (Arrow International Inc., Reading, Pa.) for central catheter placement in the right arm at the time of the cervical laminectomy with no mention of difficulty.

Because of her activity, young age, and otherwise excellent health, it was believed that the wire should be removed. Under monitored anesthesia care, the wire was surgically approached at the antecubital fossa. As it was being removed it was clear that the spiral wire was uncoiling. It fragmented both distally and proximally. Two of the three fragments were removed but the most central portion of the wire remained in the SVC. The femoral vein was cannulated, and under fluoroscopy a snare was used to remove the final portion of the wire. The patient suffered no problems during the procedures.

We have subsequently encountered another case in which difficulty advancing the guide wire/catheter was experienced during placement, with some tension on the wire noted during retrieval. On removal of the catheter and wire together, it was found that the distal end of the core wire had broken from the coil (Figure 1)—the same defect that appeared in the case of the retained wire. In this case there was no proximal fracture in the helix, and both portions of the wire were retrieved intact.

Discussion

The crux of this clinical problem is how the wire from a central catheter kit could unknowingly be left in the patient. The structure of the guide "J" wire may hold the explanation. The wire is composed of two portions. The outer tightly coiled helix is welded on both ends to a second straight core wire. The wire that was surgically removed from the patient contained only the outer helix; the core wire was absent (Figure 2).

We hypothesize that in this case there was some difficulty with insertion of the catheter (2) and guide wire, which resulted in the fracture of the weld at the distal end and a fracture of the helix at the antecubital fossa. When the guide wire was removed, the entire length of the central wire was present and the helical portion of the wire in the operator's hand was still present. Thus, it would have been very difficult to notice that only some of the outer portion of the distal

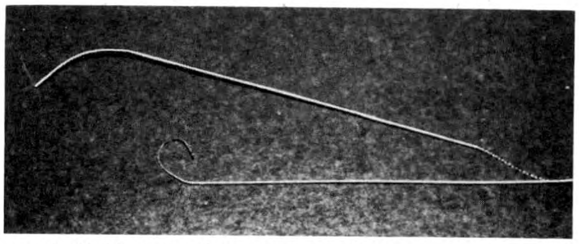

Figure 1. Guide wire from patient showing separation of the spring portion of the wire system from the end of the solid J-wire core.

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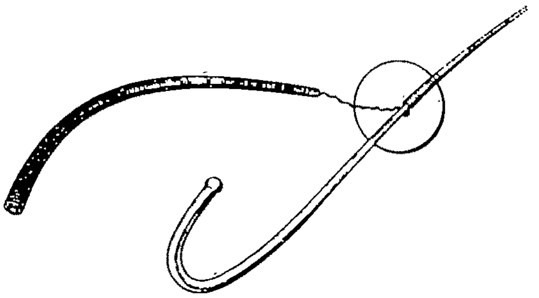

Figure 2. Drawing of the separation of the two component wires at the J-tip as occurred in the photograph. Subsequent fracture of the spring portion at a site comparable to that shown in the circle would result in retention of the helix portion as the core wire and remaining attached helix is withdrawn. We believe this is what probably happened in the first case.

part of the wire system was missing. The design of the kit prevents exposure of the J-wire to a steel needle, so shearing of the wire is an extremely unlikely cause of fracture.

There are reports in the literature of fractures of various wire devices used to insert percutaneous transluminal coronary angioplasty catheters (2) and a report of fracture of a J-wire device resulting in uncoiling of the wire (3). There has been a suggestion that the basic structure of the double J-wire system is such that fractures can result and that we should move toward single-wire coated designs (4).

From the operator's point of view, there should be a heightened concern about the integrity of the J-wire system anytime there is difficulty inserting the wire, whenever it might be kinked, and if there is difficulty in removing the wire when catheter placement is completed. Very careful inspection of the removed wire is important.

The structure of this particular guide wire is similar to nearly all other flexible guide wire kits. Prevention of this complication can be accomplished by awareness of its possibility and very careful examination of the entire wire upon removal, especially when any difficulty has been encountered upon passage.

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Anesthetic Management for the Child With Charcot-Marie-Tooth Disease

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Peroneal muscular atrophy (Charcot-Marie-Tooth [CMT] disease) is the most common cause of chronic peripheral neuropathy in childhood. This autosomal dominant disorder is manifested as distal muscle weakness and wasting that usually becomes evident by the middle teenage years and slowly progresses to include wasting of the quadriceps muscles (1). Descriptions of anesthetic management of patients with this disease are rare (2–5).

A patient is described (with a discussion of concerns regarding the anesthetic management of the child with Charcot-Marie-Tooth disease) and the anesthetic experience with this disease in our institution over the past 10 yr is reviewed.

Case Report

A 6-yr-old boy with CMT disease fell out of a tree soon after eating dinner. The only injury he sustained was a supracondylar fracture of the left humerus. He was taken to an affiliated institution that evening and was scheduled for emergency surgery to repair the fractured arm. The anesthesiologist, concerned about the underlying disease and the potential for requiring postoperative ventilatory support (without resources to provide such), suggested emergency transfer to our institution. The child had had several prior procedures without anesthetic problems. We then proceeded with emergency repair of his supracondylar humerus fracture. The surgeons requested that the patient does not receive regional anesthesia (e.g., axillary block) so that they could monitor motor and sensory functions of the limb postoperatively.

The patient underwent rapid-sequence induction of anesthesia including application of cricoid pressure after breathing oxygen. He received vecuronium (0.18 mg/kg) and thiamylal (5.4 mg/kg) intravenously, and the trachea was intubated easily. Anesthesia was maintained with O_2/N_2O/isoflurane/vecuronium while surgery proceeded without difficulty. Using a train-of-four monitor, the first return of response was noted 40 min after the initial dose of vecuronium. Surgery lasted 105 min; antagonism of neuromuscular blockade was performed with intravenous neostigmine (0.07 mg/kg) and glycopyrrolate (0.014 mg/kg) without complication. After the patient demonstrated adequate strength (i.e., sustained tetanus, train-of-four, head lift) and appropriate alertness (i.e., eyes open, responds to commands), the endotracheal tube was removed and he did well. He recovered from anesthesia in the Pediatric Recovery Unit for 105 min, was transferred to the regular ward, and was discharged home the next morning. Postoperatively, he remained hemodynamically stable and there were no signs of respiratory compromise.

Review of Anesthetic Experience

We retrospectively reviewed all operative records of children (under 16 yr of age) diagnosed with CMT disease who underwent surgical procedures requiring anesthesia in our institution in the past 10 yr by querying the medical records database system. Charts of those children who were discharged with a diagnosis including CMT disease who underwent a procedure requiring anesthesia during their hospitalization were reviewed and are reported here.

Seven patients were identified who underwent nine procedures. The details of their management are summarized in Table 1.

Several points can be recognized by reviewing the data in the table. First, none of the procedures recorded, except this case report, were emergencies, indicating the infrequency of the situation presented to us. Next, when a neuromuscular blocker was used, both depolarizers and nondepolarizers were chosen. Endotracheal intubation was common and there were no reported abnormalities of neuromuscular blockade. No adverse effects were noted from succinylcholine in particular, although monitoring for subtle effects (e.g., mild prolongation of neuromuscular

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Table 1. Patients With Charcot-Marie-Tooth Disease Undergoing Surgery From 1/79 to 12/89

Patient No.	Procedure date	Age (yr)	Procedure	ASA status	Sex	Anesth time	Anesthetic technique
1	11/1/79	16	Repair bilateral pes caves	II	F	4:35	ETT: enflurane, N_2O, STP, atropine, SCh, droperidol
2	11/21/80	13	Plantar release right foot	I	F	2:10	ETT: enflurane, N_2O, SCh, Pancur(defas)
2	10/5/84	17	Arthrodesis right foot, 1st metatarsal osteotomy	I	F	3:22	ETT: enflurane, N_2O, SCh, Pancur(defas), STP, MS, lidocaine, glycopyrrolate
3	5/2/85	12	Muscle biopsy	I	M	1:35	Mask: enflurane, N_2O, STP
4	8/30/88	12	Split posterior tendon repair, cuniform osteotomy, iliac graft, casting	I	F	3:28	ETT: halothane, N_2O, thiamylal, Pancur(paral), atropine, neostigmine; caudal: bupivacaine 0.25% with epinephrine
5	6/8/89	5	Sural nerve biopsy and lumbar puncture	II	F	1:40	Mask: halothane, N_2O, thiamylal
6	8/7/89	6	Sural nerve and muscle biopsy and lumbar puncture	II	F	1:49	Mask: halothane, N_2O, thiamylal
7	3/2/89	7	Tendon transfer, osteotomy	II	M	4:30	ETT: halothane, N_2O, Pancur(paral), atropine, neostigmine; caudal ×2: bupivacaine 0.25% with epinephrine
7	10/11/89	8	Transfer post tibialis tendon	II	M	3:15	ETT: halothane, N_2O, MS, *d*-TC(paral), droperidol, atropine, edrophonium
7[a]	4/21/90	8	Repair left humerus, radius, ulna fracture	IIE	M	1:55	ETT: isoflurane, N_2O, thiamylal, Vec(rapid seq), glycopyrrolate, neostigmine, lidocaine

ASA, American Society of Anesthesiologist Physical Status Classification; Anesth time, duration of anesthetic care for procedure (hours:minutes); ETT, endotracheal tube; N_2O, nitrous oxide; STP, sodium thiopental; SCh, succinylcholine; Pancur(defas), defasciculating dose of pancuronium; MS, morphine sulfate; Pancur(paral), paralyzing dose of pancuronium; *d*-TC(paral), paralyzing dose of *d*-tubocurarine; Vec(rapid seq), rapid-sequence paralyzing dose of vecuronium.

[a] Patient described in case report.

blockade) was not noted. Finally, we found no evidence of prolonged response to nondepolarizing neuromuscular blockers in children with CMT disease, although the sensitivity of monitoring of neuromuscular function undoubtedly varied widely. We also found no evidence of unexpected perioperative respiratory dysfunction.

Discussion

Charcot-Marie-Tooth disease is classically described as being restricted to the lower one third of the lower extremity, producing a stork-leg appearance. Insidious wasting and deformity of the hand and forearm muscles may occur later in the disease, but the arms generally remain strong. Mild-to-moderate stocking-glove sensory loss occurs in many patients, although severe disturbances are sometimes found. Treatment is limited to supportive measures, including splints, tendon transfers, arthrodeses, and various hand orthoses. Although life span is not reduced, many patients experience long-term disability. Most, however, remain ambulatory (1).

As noted previously, there are few reports regarding the anesthetic management of CMT disease in the English literature, although some reports have been published in Japan (4,5). Particular concerns in the emergency anesthetic management of this patient included safely securing the airway for general anesthesia and the potential for postoperative respiratory dysfunction. Cardiac manifestations of CMT disease include arrythmias and conduction abnormalities such as paroxysmal atrial flutter (6) and cardiomyopathy (7), although these are disputed by other investigators (8,9).

In addition, there is concern about the potential for malignant hyperthermia in patients with neuromuscular conditions. However, there is no clear evidence that CMT disease predisposes a child to having this condition, although one might consider any patient with a neuromuscular disease at increased risk of malignant hyperthermia (9).

In general, anesthesia in a child with a "full stomach" may be induced by "rapid-sequence" induction of anesthesia using succinylcholine as the muscle relaxant. However, succinylcholine can cause severe hyperkalemic reactions during the induction of paralysis in patients with progressive neurologic disorders (10–12). An alternative practice is to induce paralysis with a nondepolarizing muscle relaxant such as vecuronium (13). Although this practice has been investigated in the setting of the pediatric population (14), no studies have been performed comparing the effects of vecuronium and succinylcholine in children with neuromuscular disorders. There are case reports that describe the use of neuromuscular blocking agents in patients with CMT disease (2,4). There are, however, no reports of children (less than 18 yr old) with diagnosed CMT disease undergoing anesthesia and surgery, nor information regarding abnormalities in duration of neuromuscular blockade using larger, rapid-sequence doses of nondepolarizers in these children.

Respiratory insufficiency has been described in patients with CMT disease on the basis of respiratory muscle dysfunction (15–19). These have been older patients in whom the disease has been present for many years. Respiratory insufficiency has not been reported in children with CMT disease, although our colleague's concern regarding the possibility of a prolonged response to muscle relaxants seems warranted. In addition, pathologic evidence of phrenic nerve involvement has also been suggested (20).

The antagonism of neuromuscular blockade and recognition of adequate return of neuromuscular activity is complicated by the presence of neuromuscular disease. There are reports of paradoxical worsening of neuromuscular blockade upon attempts to reverse blockade in patients with neuromuscular disorders (21). The recovery of adequate muscular tone to sufficiently control the airway must be assessed in several ways; no one test is foolproof, although the head lift seems to be most reliable (22). In addition, the differences regarding neuromuscular immaturity and the development of the myoneural junction in children has not been addressed with respect to a specific indicator of adequacy of muscular tone after reversal of neuromuscular blockade. The fact that in many instances children are not old enough to consistently follow commands complicates this further.

In summary, we report on a child with CMT disease who presented for emergency repair of a fractured humerus. Although we were unable to document an altered response to nondepolarizing neuromuscular blockade in this child, it seems prudent to bear this possibility in mind, particularly when dealing with older patients who have had CMT disease for many years and have more cephalad progression of the disease. In addition, although succinylcholine was used in two patients without sequelae, a larger experience seems warranted before this can be recommended on a routine basis, especially as effective alternatives exist that do not pose the same risk. Regardless of technique chosen, close monitoring of respiratory function in the postoperative period is probably of particular importance in these patients.

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Opioid-Induced Spasm of the Sphincter of Oddi Apparently Reversed by Nalbuphine

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Laparoscopic cholecystectomy is a new procedure, enjoying increasing popularity and presenting new anesthetic challenges. The perioperative use of opioids in patients with hepatobiliary disease remains controversial. These drugs can cause spasm of the sphincter of Oddi, thereby complicating the interpretation of intraoperative cholangiograms (1,2). Previous studies have shown this effect can be antagonized by many drugs (1), including, most commonly, naloxone (3) or glucagon (4). We report a case in which spasm of the sphincter of Oddi, observed during intraoperative cholangiography, was probably reversed after the intravenous injection of nalbuphine.

Case Report

A 30-yr-old, 60-kg woman was scheduled for elective laparoscopic cholecystectomy after a 2-wk history of intermittent biliary colic and choledocholithiasis confirmed by ultrasonography. Her past medical history, physical examination, and preoperative laboratory evaluation, including liver function tests, were unremarkable. No preoperative medications were given. After routine anesthetic monitors were placed, morphine sulfate (15 mg IV) was given slowly over the 10 min before induction of anesthesia. Adequate sedation ensued, but the patient was still awake and denied any symptoms of biliary colic. General anesthesia was induced with thiopental (300 mg IV). To facilitate endotracheal intubation, paralysis was achieved by the administration of vecuronium (6 mg IV). General anesthesia was maintained with isoflurane (0.8%–1.0% inspired concentration) in oxygen/air (50/50). Sixty minutes after the start of the operation, the cystic artery and duct were isolated and a cholangiogram was obtained using 25 mL of half-strength radiographic contrast (Conray Mallinkrodt Medical Industries, St. Louis, Mo.). The duodenum did not fill with contrast medium and the common bile duct was occluded around the sphincter of Oddi (Figure 1). Nalbuphine (10 mg IV) was given, and 3 min later a second cholangiogram was taken using an additional 15 mL of contrast medium. Excellent filling of the duodenum was noted, as well as less constriction of the common bile duct near the sphincter (Figure 2). The operation was concluded without the need for surgical exploration of the common bile duct. The patient emerged comfortably and pain-free after the 120-min procedure. No additional analgesics were required during her uneventful 1-h recovery room stay.

Discussion

The best anesthetic for laparoscopic cholecystectomy has not been established. Arguments have been raised against the use of volatile anesthetics (5), nitrous oxide, and opioids. Nitrous oxide will cause bowel distention, which obstructs the operative field and impedes the surgery. Opioids are useful adjuncts to volatile anesthetics, but they can increase intrabiliary pressure by causing smooth muscle contraction and spasm of the sphincter of Oddi (1). During laparoscopic cholecystectomy, intraoperative cholangiography is crucial for the diagnosis of unsuspected common bile duct stones. Failure to appreciate possible opioid-induced spasm may result in misinterpretation of the cholangiogram, leading to unnecessary surgical exploration of the biliary tract with its accompanying morbidity (2).

The effects of opioids on the sphincter of Oddi are neither predictable nor consistent (6). Naloxone (3,7) and glucagon (4) have been used clinically to reverse opioid-induced sphincter of Oddi spasm. Unfortunately, both treatments have significant side effects. Naloxone may reverse intraoperative analgesia, resulting in untoward hemodynamic changes. Glucagon may produce nausea and vomiting and, as a polypeptide, may trigger an immune-mediated

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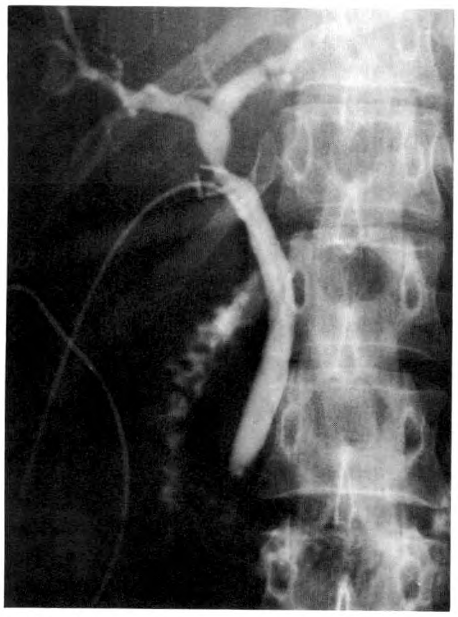

Figure 1. Initial abdominal radiograph. The cannula was advanced through the cystic duct and resides in the distal common bile duct. The intrahepatic biliary system is well visualized but note the absence of contrast in the duodenum and the narrowing of the distal common duct consistent with spasm of the sphincter of Oddi.

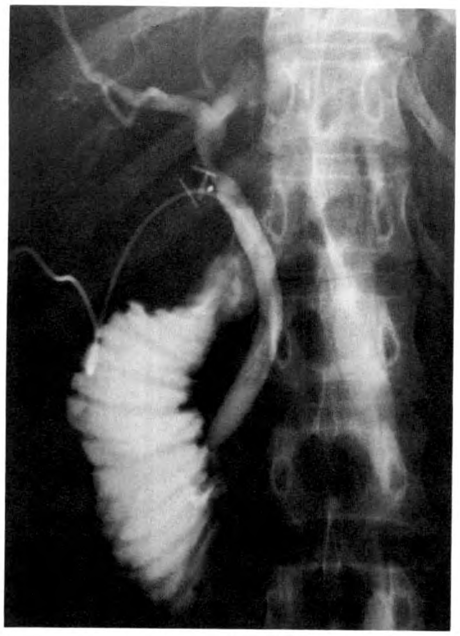

Figure 2. Subsequent abdominal radiograph taken 8 min after Figure 1 and 3 min after the administration of nalbuphine. The entire biliary system is well visualized and radiographic contrast passes freely into the duodenum.

hypersensitivity reaction associated with urticaria, respiratory distress, and hypotension (7).

Published studies regarding the action of nalbuphine on intrabiliary pressures report variable responses. Perioperative studies have shown that nalbuphine has no significant effect on the sphincter of Oddi (8–10). In contrast, two nonperioperative studies have shown that, like other opioids, nalbuphine can increase common bile duct pressure (11,12). Nalbuphine has not been studied for its ability to reverse opioid-induced spasm of the sphincter of Oddi.

Nalbuphine is classified as an agonist-antagonist drug. It acts as an agonist at the κ-opioid receptor subtype and an antagonist at the μ-receptor. It is used clinically to antagonize opioid-induced pruritus and respiratory depression (13). Therefore, we hypothesize that nalbuphine could antagonize μ-receptor-mediated biliary sphincter spasm while supplementing analgesia through its agonist effects at κ-receptors, thus avoiding some of the hemodynamic side effects associated with reversal of sphincter spasm by naloxone.

In this case, the changes demonstrated in the second cholangiogram were most likely due to reversal of the sphincter of Oddi spasm by nalbuphine. However, other alternatives should be considered. The spasm observed in the first cholangiogram was probably the result of the morphine administered before induction of general anesthesia, but other causes such as mechanical trauma during surgical dissection are possible. Opioid-induced spasm is the most likely, given the minimal trauma associated with laparoscopic as compared with open cholecystectomy. A second assumption is that the changes in the second cholangiogram were indeed the result of the administration of nalbuphine. The time relationship is the strongest evidence in support of this. Given the short (8 min) interval between cholangiograms, spontaneous recovery is unlikely as serum morphine concentration would not have decreased appreciably. However, it is possible that the cholangiographic improvement may have resulted from the mechanical effect of the second radiocontrast injection.

In summary, we report a case of opioid-induced spasm of the sphincter of Oddi evidenced by intraoperative cholangiography that appeared to be reversed by nalbuphine, thereby sparing the patient an unnecessary and potentially morbid common bile duct exploration.

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Letters to the Editor

Horner's Syndrome Associated With Brachial Plexus Anesthesia Using an Axillary Catheter

To the Editor:

This is a report of a Horner's syndrome developing after brachial plexus anesthesia using an axillary catheter.

The patient was a healthy 43-yr-old woman undergoing surgery for removal of hardware and an anterior capsulectomy of the right elbow. Brachial plexus anesthesia using an axillary catheter was planned and also intended for postoperative pain management during therapy with continuous positive motion machine.

The catheter was placed using a nerve stimulator to elicit a radial nerve motor twitch. The catheter was passed with ease a distance of 10 cm from the skin, secured with suture, and tested with three divided doses totaling 15 mL of 1.5% mepivacaine with 1:200,000 epinephrine. Paresthesias and motor weakness of the right hand and arm developed within a few minutes.

Thirty minutes later, 20 mL of 0.5% bupivacaine with epinephrine was injected through the catheter. An hour later, the patient reported mild discomfort on skin incision requiring another injection of 20 mL of 0.5% bupivacaine with prompt resolution of her discomfort. The patient was taken to the recovery room and then to her hospital room approximately 2 h later with 8 mL of 0.125% bupivacaine per hour infusing in her axillary catheter for postoperative pain management.

Later, the patient reported having a droopy eyelid, which she first noted in the recovery room but did not mention to the nurses. Close examination revealed ptosis, miosis, anhydrosis, conjunctival injection, and right-sided nasal congestion, all consistent with Horner's syndrome. The bupivacaine infusion was temporarily stopped and then restarted after reassurance that her symptoms were very likely the result of local anesthetic spread high into her neck and that they would resolve as the anesthetic given during the operation wore off. The Horner's syndrome steadily regressed even during the continuous infusion and was absent in less than 48 h. In addition, she had excellent pain relief during the 3 days the axillary catheter was in place. The catheter was removed on postoperative day 3 and noted to still be in 10 cm at the skin. X-rays after contrast injections (total of 10 mL of diluted Conray [Mallinckrodt Medical Inc., St. Louis, Mo.]) before removal confirmed proximal spread (see Figure 1).

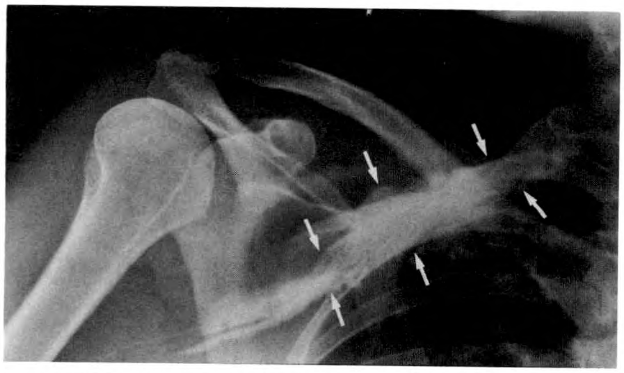

Figure 1. Right shoulder radiograph of patient shows catheter in the axillary neurovascular sheath. The sheath is distented with 10 mL of contrast solution. Note the position of the catheter tip and extensive proximal spread of the solution.

Given the extensive proximal spread of 10 mL of contrast solution, it is quite likely that the two 20-mL boluses of bupivacaine used intraoperatively spread to the stellate ganglion and resulted in the Horner's syndrome.

We report this case so that patients can be informed of the possibility of Horner's syndrome developing, a transient and uneventful side effect that should not hinder the use of the axillary catheter for postoperative pain management.

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Spinal Anesthesia and Friedreich's Ataxia

To the Editor:

We were interested in the recent report by Kubal et al. (1) concerning spinal anesthesia for a patient with Friedreich's ataxia. Their successful result was gratifying and identifies another acceptable technique for these patients; however, we would caution that a more detailed cardiac investigation might be appropriate. As was demonstrated by Child et al. (2) and illustrated by our case presentation (3), cardiac involvement, particularly hypertrophic cardiomyopathy, is found in most patients with Friedreich's ataxia and may be asymptomatic until it presents as sudden death. Our patient had significant cardiac disease and required a bowel resection for ulcerative colitis, so we used a technique of narcotic-based general anesthesia with invasive monitoring, using epidural morphine for postoperative pain control to avoid the potential risks of sudden pain-induced changes

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in peripheral vascular resistance or heart rate. We intentionally avoided neuraxial local anesthetics to minimize the effect of sympathetic blockade. The patient described by Kubal et al. had a history suggestive of greater cardiovascular stability, but echocardiography as a minimum investigation would seem advisable before general or major regional anesthesia.

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Reviewer Gets Reviewed

To the Editor:

We feel inclined to comment on Dr. Racz's recent review of our book, *Chronic Pain* (1). Our response is not a defensive reaction to criticism; submitting manuscripts for peer review on a regular basis teaches one to walk through this particular fire as a matter of course. We are dismayed at both the lack of responsible, or even reasoned, substantiation of claims he makes in the course of his review and the general tone of his commentary—more suited to a movie review in a tabloid than what is expected in a respectable medical journal. To this, we will trust and respect the more discerning nature of interested readers to form their own opinions. However, to avoid the same trap, we will elaborate on some examples from Racz's commentary to illuminate the nature of our criticism of his review.

On the subject of stellate ganglion blocks, Dr. Racz states that the anterior paratracheal (C-6 level) approach, using Chaissaignac's tubercle as a landmark, is "out of date and hazardous." This technique is so commonly and primarily described in virtually all modern textbooks on regional anesthesia and pain management that it certainly can be called "classic." While Dr. Racz stands (seemingly alone) against this technique, he offers no alternative nor a valid reference supporting either the danger of the approach we advocate or the comparative safety of his implied alternative. Based on his misinformation on stellate ganglion blocks and a misinterpretation of a standard table of maximum total doses of local anesthetics, Dr. Racz condemns this book as dangerous.

We are particularly perplexed by Dr. Racz's comments regarding the caution expressed in our text on the topic of epidural steroid injections. What other rational conclusion can be drawn by the open-minded individual who has no vested interest in supporting a potentially very lucrative but unproven procedure than to support reasonable caution in defining indications and wondering about all possible motivations for performing it? This is in the face of absolutely no well-designed, meaningful studies to support the opinion of Dr. Racz that this procedure has "saved an enormous amount of unnecessary surgery and suffering." Such an opinion expressed in the context of a book review leads one to wonder at his particular motivations. Does he protest too much?

In an admittedly less objective response to his view that our (purposefully) succinct handbook is not appropriate reading matter for training purposes, we relied on the more than 10 years of experience in the operation and instruction of students and residents-in-training at our University-based, multidisciplinary Pain Management Center, as a principal guide to both style and content.

In conclusion, we ask that a reviewer adhere to the same standards of academic integrity that are expected from authors submitting manuscripts for review. In view of these gross inaccuracies which were not detected in the editorial process, a retraction and re-review would certainly seem appropriate.

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Hare BD, Fine PG, eds. Problems in anesthesia: Chronic Pain. Philadelphia, JB Lippincott, 1990.

In Response:

Doctors Hare and Fine indeed are doing the very thing they claim they are not doing, i.e., taking personally comments and only the critical aspects of the review of their book. I stand by my comments.

Critical discussion of stellate ganglion block deserves more space than review of a 134-page book would allow. However, I think it is necessary to address the question of the safest technique for doing the block. I have done many stellate ganglion blocks over the past 25 years, and I have never used the anterior paratracheal (C-6 level) approach. The remote chance of injecting into the vertebral artery, a nerve sleeve, and/or causing a pneumothorax is far greater than if the ventrolateral side of the C-7 vertebral body approach is utilized (1). Because of the safety of this approach, we have used this technique several hundred times to inject a 3% phenol solution under fluoroscopic guidance to produce long-lasting stellate ganglion block.

Dr. Gregory Kizelshteyn presented a scientific exhibit at a major national meeting that included very elegant anatomic dissections (2) showing the unpredictable nature of the spread when the C-6 level approach is utilized. This further substantiates my position. Any standard anatomic textbook will show that the stellate ganglion is not at C-6 but at C7-T1.

The question of epidural steroids is another emotional issue. It probably is the most common procedure anesthesiologists do on pain patients. I believe that anesthesiologists do it because they want to help their patients. Anesthesiologists who use this technique do so based on clinical judgment, experience, and intentions other than just financial gains.

I do agree there are many areas, especially in chronic pain management, where we need well-controlled, double-blind studies repeated in many centers. However, even in the absence of well-controlled trials, clinical experience does support the use of epidural steroids (3).

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Dilute Local Anesthetics in Epidural Analgesic Solutions

To the Editor:

The article by Badner et al. (1) and the ensuing correspondence (2,3) shed an interesting light on what is becoming a common clinical practice. It is puzzling, however, that no discernible effect on pain after knee replacement surgery was found from the addition of 0.1% bupivacaine to the lumbar epidural fentanyl infusion. This work raises several questions pertinent to the clinical management of postoperative epidural analgesia.

Badner et al. report average infusion rates of 7–9 mL/h. How does this compare with the volume of local anesthetic required to anesthetize the operative site in these patients? A large divergence may suggest that the infusion rate was inadequate for the local anesthetic component to cover the relevant dermatomes. Moreover, prolonged epidural infusion of dilute bupivacaine solutions will produce sensory blockade demonstrable by pinprick (we have routinely obtained levels to pinprick in more than 8000 laboring patients receiving 0.04% bupivacaine in epidural infusion analgesia). Did the sensory levels achieved in these patients encompass the operative site? The potentially interesting implications of this study for the inclusion and clinical application of dilute local anesthetics in epidural analgesic solutions cannot be determined without these data.

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3. Prados W. Addition of low-dose bupivacaine to epidural fentanyl infusion. Anesth Analg 1991;73:366–7.

In Response:

We thank Dr. Youngstrom for his interest in our paper, which compared the use of 0.1% bupivacaine with epidural fentanyl (1), and the ensuing correspondence (2,3). He raises what we believe is the essential question, "What is the necessary amount of bupivacaine required to supplement the effect of epidural fentanyl?" Although quite effective in the parturient when used after a bolus and with epinephrine (4), we believe that 0.1% or lower concentrations, in fact, are ineffective in the postoperative patient when combined with 10 μg/mL of fentanyl. Our conclusion is based partly on the fact that included in our protocol were sensory examinations. Although we could assess only the contralateral limb because of dressings at the operative site, only 1 of 16 patients had a deficit to pinprick and ice involving the L3–4 dermatome. In contrast, as noted in the discussion of our paper, Raj et al. (5) required 6–15 mL/h of 0.25% bupivacaine alone to provide effective analgesia while creating a sensory block from S-2 to L-1 in a similar population of patients.

It is our impression, therefore, that the optimum concentration of bupivacaine lies between 0.1% and 0.25%.

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Use of the Laryngeal Mask Airway to Facilitate Fiberscope-Aided Tracheal Intubation

To the Editor:

It has previously been reported that it is easy to view the laryngeal aperture with a flexible fiberscope through a laryngeal mask airway (LMA) (1–7). This fiberscope/LMA experience suggests that the LMA would greatly facilitate a fiberscope-aided tracheal intubation, and I have found this to be the case in the adult patient.

After general anesthesia is induced, the lungs are ventilated via a conventional anesthesia mask (a standard oropharngeal is inserted as needed) with a halogenated

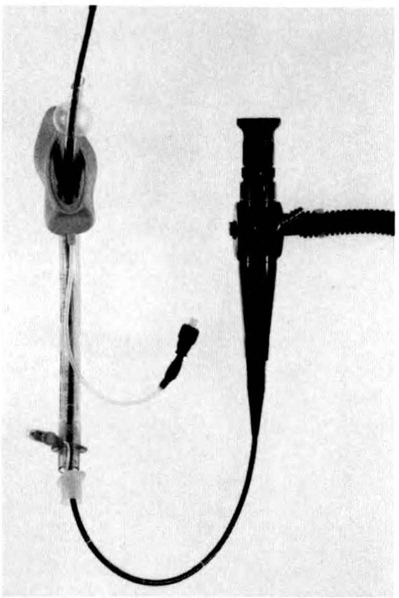

Figure 1. Fiberscope within a 6.0-mm-ID ETT that is within the shaft of a number 4 laryngeal mask airway. The fiberscope and ETT pass through the central compartment of the grille at the end shaft of the laryngeal mask airway, and the cuff of the endotracheal tube is inflated to increase the distinctiveness of the ETT.

Table 1. Largest Size Endotracheal Tube and Fiberscope That Can Fit Concentrically Into the Laryngeal Mask Airway

LMA size number	Largest ETT that fits into LMA, (ID in mm)	Largest fiberscope that fits into ETT, listed in column (OD in mm)
4	6.0, cuffed	5.0[a]
3	6.0, cuffed	5.0[a]
2	4.5, without cuff	3.5[b]
1	3.5, without cuff	2.7[c]

LMA, laryngeal mask airway; ETT, endotracheal tube; ID, inside diameter; OD, outside diameter.

[a] Olympus BF-P20D.

[b] Pentax FB-10H or FI-10P.

[c] Olympus PF-27M.

drug in balance oxygen until a depth of anesthesia adequate for tracheal intubation is achieved. A number 3 or 4 sized LMA is then inserted and the lungs are ventilated via the LMA. The anesthesia circle system is then disconnected from the LMA and a fiberscope, with the proximal end jacketed with a well-lubricated, adaptorless, 6.0-mm-ID endotracheal tube (ETT) (this is the largest sized ETT that will fit through the shaft of the number 3 and 4 sized LMA), is inserted into the shaft of the LMA and through the central compartment of the grille at the end of the shaft, the vocal cords, and on into the trachea. The 6.0-mm-ID ETT is passed over the fiberscope into the trachea (see Figure 1), the fiberscope is withdrawn, the adapter to the ETT is reinserted, the cuff of the ETT is inflated, and the lungs are ventilated via the ETT. A suture is put through the wall of the proximal end of the ETT, and the loose ends of the suture are taped to the forehead to stabilize the ETT within the LMA. The laryngeal aperture has been easy to view with minimal manipulation of the fiberscope in all cases to date, and the ETT has easily passed into the trachea. During surgery the cuff of the LMA is deflated to a low pressure. The ETT is removed from the LMA at the end of surgery, the lungs are ventilated via the LMA, and then the LMA is removed before the patient enters stage II of general anesthesia. A standard oropharyngeal airway can replace the LMA as needed.

This intubation technique is unlikely to work well when it is difficult to ventilate the lungs via the LMA because, in this circumstance, it is likely that the LMA is not well situated over the laryngeal aperture or the laryngeal aperture is blocked by the epiglottis or tongue (2,3,6,8,9). With either cause of difficult LMA ventilation, it may be difficult to direct the fiberscope into the trachea. Further significant limitations to the method consist of the need to use a number 3 or 4 sized LMA (may not fit into all adult patients) and the need to use a 6-mm-ID ETT (which may be unacceptably small in some patients). Table 1 shows the largest sized ETT and fiberscopes that can concentrically fit inside the various sized LMAs.

This intubation technique is likely to be uniquely valuable in a few situations. First, and most importantly, this technique may be especially useful when a "cannot intubate, cannot ventilate via mask" situation develops (10). In this catastrophic circumstance, use of the LMA (as outlined) may solve both the mask ventilation and intubation problems. Second, when just a "cannot intubate under general anesthesia" situation develops (the lungs can still be ventilated via conventional mask), the LMA may still serve as an excellent airway intubator for the fiberscope (10). Third, the technique greatly facilitates viewing of the vocal cords during and at the end of neck surgery (4,7). Fourth, the technique is useful when a diagnostic view of the laryngeal aperture and/or trachea is necessary before or simply without ETT intubation (1,5).

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A Technique for Reducing Pain Associated With Propofol Administration

To the Editor:

Propofol has achieved widespread acceptance around the country since its introduction in 1989. One continuing problem associated with the use of this drug is its tendency to cause aching upon administration. A technique that has not been previously reported involves minimizing the volume of drug/intravenous fluid diluent administered for any selected drug infusion rate. When propofol is introduced into an intravenous line, increasing diluent flow increases the pain associated with injection. This clinician has found that there is significantly less pain on administration of propofol if the carrier IV is turned off completely and only undiluted propofol is infused. This technique is not perfect, but except in very small veins or particularly sensitive individuals, injection of up to 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of propofol is accepted quite well. It is not obvious why the same infusion rate of propofol causes less pain on administration if its volume is minimized. One possibility is that the smaller volume decreases the contact area between vein endothelium and drug and that contact area is a more important determinant of pain than is drug concentration.

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Empty the Stomach by Endoscopy Before Pyloromyotomy

To the Editor:

Thank you for publishing Suresh's anecdote (1). In the last year, 15 of 18 neonates with pyloric stenosis had operations performed by one surgeon (Mr. D. E. Sibson), who performs an endoscopy just before anesthesia and surgery.

With the child awake, swaddled, on its left side in an incubator, a 9-mm endoscope is passed into the stomach. The endoscope is used to confirm the diagnosis (the pylorus does not open) and empties the stomach under direct vision.

The child is moved to the operating table, breathes oxygen, and anesthesia is induced intravenously without a nasogastric tube or succinylcholine and optional cricoid pressure. Atracurium is used to facilitate endotracheal intubation; the endoscopy provides a tachycardia so atropine is not used even for its drying action.

Reflux through the pylorus from the duodenum is unlikely, and knowing the stomach is empty relaxes the minds and not the sphincters of occasional neonatal anesthetists.

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Reference

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Continuous Arterial Pressure Monitoring During Magnetic Resonance Imaging—An Alternative Method

To the Editor:

The challenge of managing acutely ill patients during magnetic resonance imaging (MRI) procedures is increasing as MRI units are being widely installed throughout the United States. The presence of a 1.5-T magnetic field necessitates the removal of ferromagnetic materials from the suite because of danger to the patient or problems with signal acquisition. Arterial blood pressure has been monitored manually by palpation, by Doppler (1), and by oscillotonometric devices (2), such as the Dinamap model 1846SX/P (Criticon). However, the pumping operation of the instrument may produce radiofrequency interference during magnetic resonance acquisition, necessitating manual cycling of the instruments while the magnetic resonance acquisition is paused (3).

We report a simple and effective means of continuous arterial blood pressure monitoring. Although the concept of water manometry is not new, the application of this concept for measuring arterial blood pressure in the MRI suite has not been reported. At our institution we are frequently called upon to administer general anesthesia for stereotactic radiosurgery, which requires induction of general anesthesia and endotracheal intubation before placement of the patient in a stereotactic head cage for MRI scanning. Induction of anesthesia takes place outside of the MRI suite, where a full compliment of monitors and tools may be used, including electronic arterial monitoring. On movement to the MRI suite, the patient is placed on a Mongahon 225 volume ventilator, and total intravenous anesthesia is maintained. The electrocardiogram is monitored remotely with a Hewlett Packard 78352A monitor, and a Nonin Medical Corporation 8604 pulse oximeter is utilized. To monitor blood pressure, a standard water manometer (Medex, Inc.) with stopcock is attached to the stopcock next to the transducer of a Baxter electronic pressure monitoring kit. The arterial pressure tubing from the patient to the transducer is approximately 200 cm in length, thus allowing the transducer to be placed up to 200 cm vertically above the level of the left atrium. We find it convenient to tape the device to the front of the MRI scanner. As the density of mercury is 13.6 times the density of H_2O, a column of saline 136 cm high equals 100 mm Hg. The length of the manometer is 40 cm and therefore has a range of approximately 30 mm Hg. Thus, the manometer may be positioned at a height above the patient to allow measurement of mean arterial blood pressure between 80 and 110 mm Hg. If the pressure is lower or higher than the set range, the device may be lowered or raised accordingly so the pressure remains within the manometer range. The tubing and manometer are filled with heparinized saline (2 U/mL) from the pressurized transducer apparatus. The turn of a stopcock allows the device to be occasionally irrigated in the usual manner to prevent thrombus formation. The standard pressure infuser bag (Medex), with the aneroid pressure gauge removed and the hole capped with a standard needle cap, is used. The red float in the manometer is easily visible on top of the clear heparinized (2 U/mL) saline column. This system allows easy, simple, continuous, and reliable measurement of heart rate (pulsation of the red float) and mean arterial blood pressure in a setting hostile to modern sophisticated monitoring devices.

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Droperidol Prevents Serotonin-Induced Bronchospasm, Pulmonary Hypertension, and Intrapulmonary Shunt

To the Editor:

In a recent article, Gentil et al. (1) suggested that droperidol antagonized serotonin-induced bronchospasm in an experiment using guinea pigs. Serotonin increases the pulmonary arterial pressure and the intrapulmonary shunt as well as the bronchial muscle tone. We found in dog studies that injection of 0.5 mg/kg of droperidol reversed both pulmonary hypertension and increased intrapulmonary shunt that were caused by continuous serotonin administration at a rate of 50–100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (2). Serotonin produces a biphasic concentration vasoactive effect (3). At low concentrations serotonin acts directly on a specific serotonin receptor that is not antagonized by α-adrenergic blocking agents (1,3,4). High concentrations of serotonin, however, produce vasoconstriction by activation of an α-adrenoceptor that is antagonized by α-adrenergic blocking agents (3,5). We used high serotonin doses that were 8–16 times that of Gentil et al. because this infusion rate was needed continuously to increase by twofold the mean pulmonary arterial pressure (6). We demonstrated that phenoxybenzamine (2 mg/kg) reversed serotonin-induced pulmonary hypertension and increase of intrapulmonary shunt (7). We also found in our preliminary study that droperidol pretreatment failed to increase pulmonary arterial pressure with low doses of serotonin. From these results, we suggest that droperidol reverses not only serotonin-induced bronchospasm but also pulmonary vasoconstriction by antagonizing a specific serotonin receptor.

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Propofol and Pharmacokinetic Modeling

To the Editor:

We read with interest the recent study by Stokes and Hutton (1) on rate-dependent induction phenomena with propofol. Certainly we would agree with the authors' aim of stimulating greater consideration of biophase characteristics in pharmacologic modeling. In this context, though, several points need to be raised.

First, the end point of the study seems too vaguely defined; we are told nothing of the sampling rate or technique for ascertaining loss of verbal contact. How was this end point standardized and made reproducible? We would suggest that "loss of verbal contact" as described is too variable an end point for the purposes of a dose-response curve upon which to base pharmacologic modeling. Electroencephalographic and evoked potential

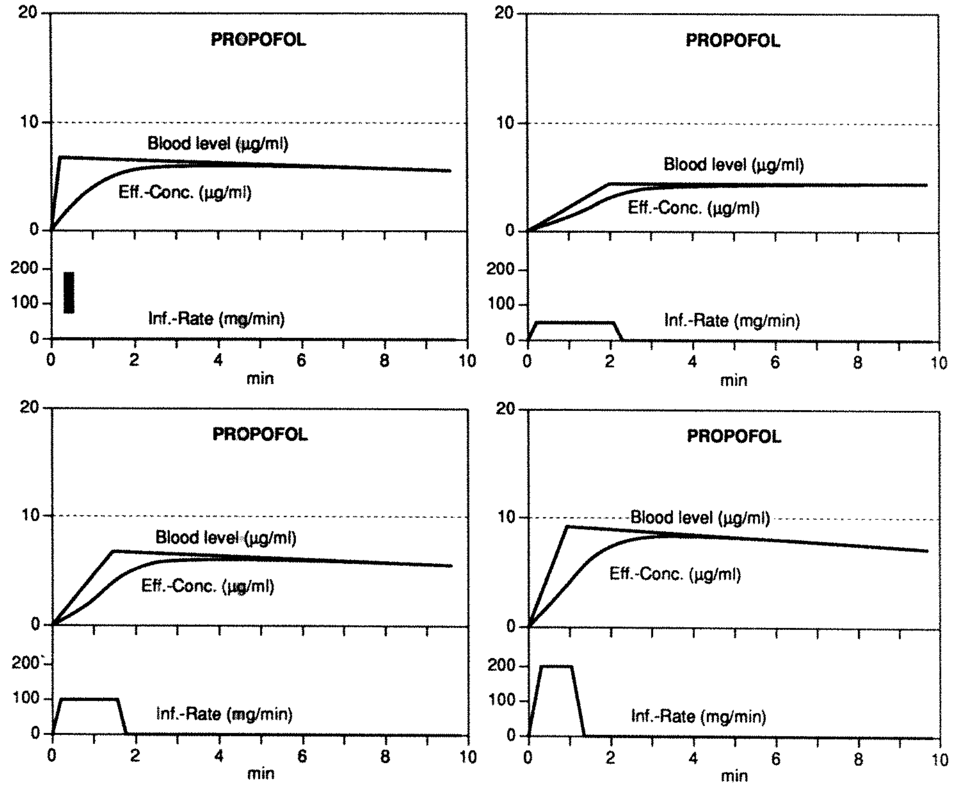

Figure 1. Modeling of infusion and bolus schemes.

measurements (2)—methods of quantifying biophase pharmacodynamics now readily available—would perhaps provide a more objective and quantifiable end point.

Second, in studying any system with linearly increasing characteristics at fixed sampling intervals, the group with the steepest time-slope is bound to show the greatest experimental or methodical error (overshoot). The longer the interval between sampling, the larger this slope-dependent end-point detection delay will be. Might not such a simple methodical explanation go some way toward explaining the results obtained?

Third, the authors assume that rapid administration of propofol "leads to an early peak in plasma concentration providing a large gradient for both uptake into the central nervous system (CNS) and for drug redistribution to other tissues." Modeling these induction schemes according to a three-compartment model based on a large patient data base (3,4), it is evident (Figure 1) that plasma levels are maximal at the end of the induction procedure for all four schemes: there is no early plasma peak as such. According to the authors' own results, there was no significant difference in the (mean) blood propofol levels at the end of the induction procedure.

There thus seems little basis for assuming that a *rate-limiting* transfer rate into the biophase explains the differing behavior of the groups in the study. On the contrary, with the results obtained it seems likely that transfer out of the circulation into the biophase (and other compartments) for propofol is rapid—and perhaps related to injection speed overpressure after all. Under such circumstances, the major differences between the groups would be differences in biophase or other compartment concentrations: faster injection merely fills these compartments more rapidly without producing large differences in blood concentration. The resulting higher *biophase* concentrations would produce more cerebral depression ("depth of anesthesia"): a condition not detectable by this study design involving the simple on-off phenomenon of loss of verbal contact. Further studies involving objective quantification of biophase activity to clarify current definitions of absolute and relative drug potency are clearly needed.

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Propofol and Malignant Hyperthermia

To the Editor:

I read with interest the letter to the editor by Dr. Gallen regarding the uneventful usage of propofol in a malignant hyperthemia (MH)-susceptible patient (1).

Although MH did not develop in this particular patient during the described anesthetic administration, I believe that Dr. Gallen should have tempered his enthusiasm and phrased his conclusions in a more appropriately conservative manner.

One observation or case report should never be the basis to *confirm* any conclusion or suggestion. In light of the unpredictable nature of MH, Dr. Gallen's report of a single case should be viewed as *supporting* the conclusion of Raff and Harrison (2). In this respect, Dr. Gallen's concluding sentence would be more appropriate if worded as "This case *supports* the suggestion based on animal experiments (2) that propofol *may be* safe in MH-susceptible patients and *may* offer a valuable alternative in the anesthetic management of these patients."

This is my personal opinion and does not necessarily reflect those of the Department of the Navy.

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The Gum-Elastic Bougie: A Life Saver

To the Editor:

The gum-elastic bougie (1), although not a new device, continues to prove its usefulness. The following case report demonstrates the benefits to be gained from having this device readily available in the operating room.

A 32-yr-old woman was admitted in established labor at 40-wk gestation. Physical examination was remarkable for morbid obesity, the body weight being 454 lb (206.36 kg) with a height of 5 ft 1 in (152.5 cm)—4.34 times the ideal body weight (Broca's Index). Anesthesia service described the patient as potentially being difficult to intubate because of limited movement of the cervical spine; her short, fat neck; and large breasts. Aspiration prophylaxis (famotidine and metoclopramide) was ordered in addition to the Bicitra administered on admission to the labor and delivery suite to facilitate awake intubation under local anesthesia should the patient require cesarean section.

Labor progressed uneventfully for several hours, when fetal distress became apparent from variable decelerations on cardiotocographic monitoring confirmed by decreased scalp pH. The patient was immediately brought to the operating room for emergency cesarean section. The urgency of the situation precluded awake fiberoptic intubation, therefore awake direct laryngoscopy was planned. On questioning the patient and nursing staff, it became apparent that the usual drugs to minimize the chances of aspiration of gastric contents had not been given, therefore it was believed that the safest option was to proceed without topical anesthesia, and this was explained to the patient. Only the epiglottis was visible at laryngoscopy and an initial attempt at tracheal intubation was unsuccessful. A gum-elastic bougie was then inserted immediately posterior to the epiglottis and caused the patient to cough, suggesting correct placement. An endotracheal tube was quickly passed over the bougie and into the trachea, confirmed by capnography. Anesthesia was induced and surgery proceeded uneventfully resulting in the delivery of a healthy female child with Apgar scores of 8 and 9.

The gum-elastic bougie undoubtedly contributed to the good outcome in this case. Without it, intubation could potentially have been much more difficult, and significant fetal hypoxia could have occurred.

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Reference

1. Macintosh RR. An aid to oral intubation. Br Med J 1949;1:28.

Oliguria Due to Obstruction of Urine Bag Filter (Terumo Uroguard)

To the Editor:

We recently encountered a patient who had oliguria owing to difficulty with a urine bag during surgery. A 5-yr-old patient (20 kg) with no medical problems except chronic otitis media underwent a tympanoplastic operation. The patient was anesthetized with enflurane (2%), nitrous oxide (65%), and oxygen. About 1 h after uneventful anesthesia, we found no urine being excreted into the urine bag, although only a small amount of urine was observed in the catheter. Vital signs were within normal ranges. Systolic arterial blood pressure was 110 mm Hg, heart rate was 90 beats/min, and body temperature was 36°C. We initially suspected hypovolemia and administered an infusion of lactated Ringer's solution at a rate of about 10 $\mathrm{mL \cdot kg^{-1} \cdot 30\ min^{-1}}$. We then checked the route of the urinary catheter and found no kinking; pressure on the lower abdomen yielded only 5–10 mL of urine. Finally, a test dose of furosemide (2 mg IV) was administered 2 h after the start of the operation and resulted in no further urine excretion. When the urine bag was picked up to change the urinary catheter, an air filter accidentally popped off the bag (Terumo Uroguard) (Figure 1). A considerable amount of urine was excreted immediately afterwards. We referred this to the manufacturer (Termo Co. Ltd., Tokyo, Japan) who found mechanical obstruction of the air filter. This case

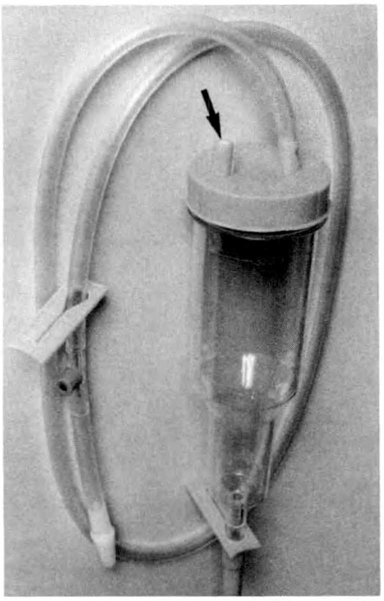

Figure 1. Mechanical obstruction of air filter (*arrow*) in the urine bag (Terumo Uroguard).

illustrates that when one encounters poor urine excretion without any obvious cause, the catheter should be replaced without hesitation.

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A Potential Defect in an Ohmeda Sevotec III Vaporizer

To the Editor:

Although there have been few reports regarding potential problems with vaporizers (1), we recently experienced a potentially dangerous problem in a new Ohmeda Sevotec III vaporizer. A 2-yr-old boy (10 kg) was scheduled to have orthopedic surgery for bilateral club feet. About 30 min after injection of scopolamine (0.1 mg IM), anesthesia was induced with increasing concentration of sevoflurane combined with 65% nitrous oxide and 32% oxygen by mask. After 5 min he appeared to be asleep and insertion of an intravenous line was attempted. However, the patient suddenly started to cry. Increasing the concentration of sevoflurane to 5% did not induce unconsciousness. We abandoned sevoflurane anesthesia after checking the gas mixture ourselves and found the aroma of the sevoflurane to be very weak. We switched to isoflurane (2–3%), which resulted in satisfactory anesthesia. After the operation, we analyzed the concentration (vol %) of sevoflurane coming out of the Sevotec III. A poor correlation was found between the dial setting (%) and the concentration (vol %) obtained with a gas analyzer (Rascal). A 1% dial setting corresponded to 0.32% (vol %) by gas analyzer and 5% corresponded to 0.8% (vol %), respectively.

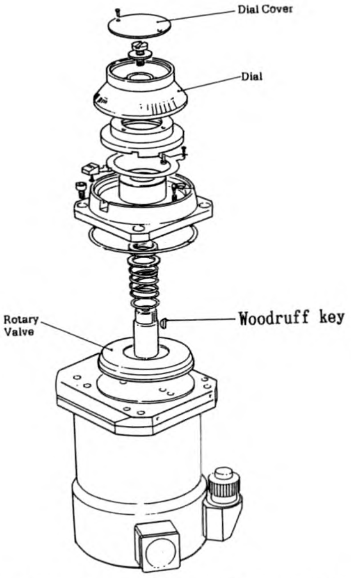

Figure 1. Dial and rotary valve assembly in an Ohmeda Sevotec III vaporizer.

As a problem in the vaporizer was suspected, we requested that the manufacturer check the vaporizer. The cause of the trouble was a missing woodruff key (Figure 1). Usually, the rotary valve activates the dial by a woodruff key. The dial and the rotary valve will not contact each other without the key. It is unclear why the woodruff key was missing as the vaporizer had never been taken apart. We, fortunately, discovered the vaporizer problem because of the use of a slow induction of anesthesia. If the vaporizer had been used on an adult patient after a rapid induction of anesthesia, the problem may have been masked by adjuvants, such as muscle relaxants. Consequently, when it is difficult to anesthetize a patient by an inhaled anesthetic, one should check the circuit. A gas analyzer will also detect this type of failure.

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Reference

1. Goldman DB, Mushlin PS. Leakage of anesthetic agent from an Ohmeda Tech IV vaporizer. Anesth Analg 1991;72:567.

Section Editor
Norig Ellison

Book Reviews

Critical Care Practice

John W. Hoyt, Alan S. Tonneson, and Steven J. Allen, eds. Philadelphia: W.B. Saunders, 1991, 571 pages, $45.00.

In the United States, anesthesiologists were heavily involved in efforts to introduce critical care medicine as a distinct clinical specialty. Although much of the early emphasis of anesthesiologists was focused on respiratory problems as the central issue in most critically ill patients, it was clear from the outset that as a medical subspecialty, critical care medicine encompassed much more. At present, a major issue is the absence of a good definition of the limits of this subspecialty. One approach has been to define this field in terms of resuscitation, similar to the stepwise approach to cardiopulmonary resuscitation used by the American Heart Association in basic and advanced life support algorithms. To this end, the Publications Committee of the American Society of Critical Care Anesthesiologists have published *Critical Care Practice*. This book, comprised of 31 chapters and 571 pages, is intended to serve as an introductory text for house officers and fellows during their time spent in the ICU.

This is a multiauthored text whose editors are well known for their many past teaching and research contributions to critical care anesthesiology. They have divided the book into three sections dealing with critical care life support, organ system failure, and specific critical care topics. These topics are covered by 44 authors, about half of whom are among present leaders in anesthesiology and critical care medicine and most of whom are known for their teaching and communicating skills.

This is a broad-based book, which is primarily directed toward anesthesiologists in-training but will serve as an introductory text for other medical specialties as well. Particularly well done are the algorithms for early stabilization of respiratory, cardiac, and neurologic injury. Further, the material contained in this book often covers more than might be expected from an introductory text. The entire section dealing with specific problems in multiorgan system failure, an area of increasing interest, is well done, given space limitations in an introductory text for such an all-encompassing subject. There are in-depth discussions of ethical considerations, triage responsibilities, pain management, and the somewhat uncertain role of anesthesiologists in the critical care milieu.

The information presented is up to date with more than a third of the bibliographic references being from 1985 to the time of publication. In many chapters, bibliographic material is indexed with headings as to subject. In others, for reasons unclear to this reviewer, indexing is not used. Numbers of references per chapter range from more than 90 down to three, in which case all three were to other texts.

As with many multiauthored texts, some unevenness in depth, style, and content of chapters occurs. As an example, metabolic acid-base disturbances are covered in three pages, whereas 17 are devoted to capnometry and pulse oximetry. In some sections, the information presented does little more than provide background information instead of describing an algorithm for care delivery. As one example of this, in the chapter dealing with care of patients after organ transplantation, fully two-thirds of the chapter is devoted to technical aspects of surgical procedures used in transplantation, whereas four pages are left for specifics of preoperative and postoperative care of organ transplantation patients. Despite these minor failings, this book is well worth its modest price, and will more than adequately serve for its intended purpose as an introductory text in critical medicine for house staff in anesthesia and other specialties. The editors are to be commended on their efforts to set a standard.

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Vascular Anesthesia

J. A. Kaplan, ed. New York: Churchill-Livingstone, 1991, 717 pages, $94.95.

This reviewer is delighted to see that vascular anesthesia is being recognized as an important subspeciality in anesthesiology as evidenced by the number of textbooks published in recent years. *Vascular Anesthesia* is arranged under four sections with 23 chapters written by 44 authors.

Section I (three chapters) deals with preoperative assessment and management of the vascular surgery patient. Cardiac risk assessment, optimization of the cardiovascular system, and radiology of the vascular system are covered in this section. Section II (four chapters) covers cardiovascular physiology and pharmacology.

Section III (12 chapters) emphasizes specific anesthetic considerations. This section covers specific surgical procedures such as carotid artery, thoracic and abdominal aorta, peripheral vasculature, liver transplantation, and pediatric vasculature, as well as monitoring during surgery, regional versus general anesthesia for vascular surgery, and hematologic considerations in vascular surgery. Section IV (four chapters) deals with postoperative management. Included here are postoperative pain management and postoperative complications and management.

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This is a well-written and well-edited textbook and the quality of the material, the manner of presentation, and the references are uniformly excellent. However, in future editions, this reviewer would like to see more complete presentations of anesthesia for ruptured abdominal aneurysms, differences in hemodynamic changes with aortic cross-clamping between aneurysmal disease and aortoiliac occlusive disease, blood-conservative techniques, and anesthesia for portal hypertension surgery. Additionally, a chapter on the indications, contraindications, timing of some of the common surgical procedures, alternative techniques available, and types of grafts available written by a surgeon would help anesthesiologists to understand better the management of these patients from the surgeon's point of view.

Despite these reservations, this book is highly recommended to all those who are involved in the care of the vascular surgery patient.

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Atlas of the Difficult Airway

Martin L. Norton and Allan C. D. Brown. St. Louis, Missouri: Mosby Year Book, 1991, 214 pp.

Airway management has been considered the anesthesiologist's area of expertise. The difficult airway, especially if unanticipated, can cause fear in even the most experienced anesthesiologist. Recent analysis in the ASA closed claims study of adverse respiratory events points to inadequate ventilation, esophageal intubation, and difficult intubation as the most common causes of brain damage and death under anesthesia. Difficulty in airway management contributes to all these categories of adverse events. Better monitoring can only reduce a small percentage of these outcomes. Anticipation of difficulty with appropriate plans and alternatives may be of additional help. Drs. Norton and Brown have combined their experience in the Difficult Airway Clinic at the University of Michigan at Ann Arbor to give us an approach to the evaluation, definition, and management of the difficult airway. The recommendations are primarily those of the editors with contributions by their colleagues in related disciplines such as pulmonology, radiology, otorhinolaryngology, and oral surgery.

The book begins by reviewing the techniques and equipment suggested for normal endoscopy and intubation. The consultation procedures of their Difficult Airway Clinic are described including evaluation forms and flow charts. There are several chapters addressing in detail the modalities used to evaluate the structural anatomy and function of the difficult airway. The authors then turn to specific groups of patients at risk for airway difficulties. These include those with boney and soft tissue anomalies (both congenital and acquired), burns, obesity, and sleep apnea. There are separate chapters addressing the pediatric difficult airway and airway problems in oral/maxillofacial surgery. The final chapter deals with the anesthetic management of patients with a compromised airway. Such issues as transport, premedication, monitoring, and positioning are discussed as well as anesthetic induction techniques with a difficult airway.

There are abundant illustrations including black and white photographs and illustrative drawings. Airway anomalies may be one area of discussion in which a picture may truly be worth a thousand words. There are pictorial as well as textual descriptions of many of the suggested evaluation and management techniques. The book details the seemingly infinite variety of airway difficulties that can occur with emphasis on evaluation and management of the anticipated difficult airway. The problem of the unanticipated difficult airway is considered only superficially. The text may prove most useful to those presented with an uncommon airway problem in planning strategies for management. Although some note is given to "escape routes," failed-intubation protocols are not discussed in detail.

The chapters on preoperative evaluation methods provide a detailed descriptive reference. However, they rely on examinations and information not readily available or easily obtainable outside highly specialized institutions. The chapters on the pediatric difficult airway and the anesthetic management of the difficult airway provide a good overview for all persons, both practitioners and trainees, involved in airway management and intubation.

The material contained in the chapters on specific problems and management techniques will prove more clinically relevant to those outside the academic setting. With the excellent pictures and diagrams, this book will make a useful addition to the anesthesia department reference library.

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Neuroanesthesia: Handbook of Clinical and Physiologic Essentials

Philippa Newfield and James E. Cottrell, eds. Boston: Little, Brown, 1991, 458 pages, $53.25.

The second edition of this outline-style handbook of neuroanesthesia was published 7 years after the first with the same editors. The book was written by 31 authors representing 19 institutions. The largest number of authors from one institution is seven from State University of New York Health Science Center at Brooklyn College of Medicine. Twenty-six of the authors are anesthesiologists, three are neurosurgeons, one a radiologist, and one an otolaryngologist. Many of the authors are well known and are considered experts in their respective areas. There are a few additions to or deletions from the author list of the first edition, but overall there is continuity between the two editions.

The second edition consists of 17 chapters, the same as the first edition. None of the chapters is fundamentally new. The current edition has 377 pages of text and is divided into three logical sections: General Considerations containing four chapters in 84 pages (22% of text); Intensive Care, three chapters in 68 pages (18% of text); and Anesthetic Management, 10 chapters in 225 pages (60% of text).

There are 961 references cited in the book. The number of citations per chapter is, however, not uniform and ranges from 15 in the chapter on neuroradiologic procedures to 216 in the chapter on cerebral damage and pharmacologic intervention. Of the references cited, 18% are from the past 5 years, 42% from the past 10 years, 45% from 1971 to 1980, and 13% from 1970 or earlier.

The chapters are also nonuniform in the number of current references cited. The chapters on cerebrovascular lesions and tumors in the pregnant patient, posterior fossa procedures, and pediatric neurogenic airway and swallowing disorders have no references from the past 5 years, and that on transsphenoidal procedures has only one reference from the past decade! In contrast, 61% of the references in the chapter on fluid management are from the past 5 years, and 93% from the past 10 years. The majority of chapters, however, have 20%–30% of references from the past 5 years and 50%–60% from the past decade. Too many recent works are missing from the reference lists to consider the book a comprehensive and complete look at neuroanesthesia.

The second edition of this book is generally "tightened" up and better referenced than the first. There are a few additions and deletions to the text (mostly a word or sentence change), but 80%–90% of the text appears to be word-for-word exactly as the first edition. Nevertheless, the chapters appear fairly up-to-date even with these small changes. However, an occasional anachronistic statement creeps in, as in the chapter on posterior fossa procedures. The discussion of end-tidal nitrogen monitoring assumes the unavailability of a "room dedicated" gas monitor capable of measuring nitrogen. This is simply not true.

The chapters on fluid management, spinal cord injury, and pediatric neurosurgery are pleasant exceptions to the not-much-new attitude of the other chapters. Each of these chapters appears to have been significantly rewritten for the second edition. Perhaps this is to be expected as these chapters have new coauthors.

In summary, the second edition of this book is more like a supplement to the first edition than a truly new work. Most of the chapters are updated in a rather terse fashion. Importantly, however, the book is fairly current. The quality and completeness of the chapters is variable. However, this reviewer's overall impression of the book is favorable. If you like the outline-style book, and are not concerned with obtaining a comprehensive text, this is a good choice. It is particularly a good choice for a resident during a rotation on neuroanesthesia. The moderate price of $53.25 makes this book a worthwhile option for those desiring a neuroanesthesia text for their personal library.

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Pain and Central Nervous System Disease. The Central Pain Syndromes

K. L. Casey, ed. New York: Raven Press, 1991, 290 pages, $92.00

Central pain syndromes (CPS) have received all too little attention for such an important group of disorders. This is only the second text ever published on CPS, and thus it becomes an important resource for all practitioners managing patients with such afflictions.

This book is a compilation of invited essays from the first symposium held on CPS. The 21 chapters are written by renowned experts from around the world. Thus, the book is a current statement on the opinions and theories regarding the pathophysiology of CPS and the recommendations for treatment.

The text is divided into five sections, sequentially dealing with (1) the historical background and clinical description of CPS, (2) behavioral issues, (3) anatomy and physiology, (4) pharmacology, and (5) treatment modalities relevant to CPS. Most chapter bibliographies contain references from 1987 onward, so the book reflects contemporary analysis. Unfortunately, as in many multiauthored texts, writing styles vary from chapter to chapter. On the other hand, there is little redundancy which is also often seen in multiauthored texts. Tables and figures are supportive of the text with a fair representation of original figures. The book may be considered to be a bit overpriced.

Though an important work, this book will be of minimal interest to the practicing anesthesiologist. For those practicing pain management, the book is an excellent resource. Unless the anesthesiology-based practitioner has a keen interest in neuropathic pain, the book will seem a bit too overbearing. Similarly, fellows and those in-training will find many aspects of the book to be a bit arcane.

In summary, this text is an important statement of the current understanding of CPS. As the book is written mainly by neurologists, neurophysiologists, and neurosurgeons, its content and writing style may be of only passing interest to the practicing anesthesiologist. For the academic anesthesiologist involved in pain management, the book is an excellent resource on a specialty topic. Be forewarned, however, this book is not for the uninitiated.

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Boston, Massachusetts

Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Benumof JL, Saidman LJ, eds. *Anesthesia and Perioperative Complications.* St. Louis: Mosby Year Book, 1992, 694 pp, $99.00.

DeCastro J, Meyndier J, Zenz M. *Regional Opioid Analgesia.* Boston: Kluwer Academic Publishers, 1991, 633 pp, $195.00.

Duke PC, ed. *Myocardial Ischemia and Performance.* Volume 9, No. 3 of

Anesthesia Clinics of North America. Philadelphia: W. B. Saunders, 1991, 286 pp, $74.00 annual subscription for four issues.

Fry D, ed. *Multiple System Organ Failure*. St. Louis: Mosby Year Book, 1991, 407 pp, $79.00.

Janisse T, ed. *Pain Management of AIDS Patients*. Current Management of Pain Series. Boston: Kluwer Academic Publishers, 1991, 121 pp, $135.00.

Longnecker DE, Murphy FL, eds. *Introduction to Anesthesia*, 8th edition. Philadelphia: W. B. Saunders, 1991, 495 pp, $37.00.

Lyerly H, Gaynor JW, eds. *The Handbook of Surgical Intensive Care*, 3rd edition. St. Louis: Mosby Year Book, 1991, 915 pp, $26.95.

Miller RD, Kirby RR, Ostheimer GW, Roizen MF, Stoelting RK. *The 1991 Year Book of Anesthesia*. St. Louis: Mosby Year Book, 1991, 398 pp, $57.95.

Paris WCV, ed. *Contemporary Issues in Chronic Pain Management*, Boston: Kluwer Academic Publishers, 1991, 311 pp, $115.00.

Raj PP, ed. *Practical Management of Pain*, 2nd edition. St. Louis: Mosby Year Book, 1992, 1096 pp, $145.00.

Sandoe E, Sigurd B. *Arrythmia—A Guide to Clinical Electrocardiology*. Bingen/Rh, Germany: Publishing Partners, 375 pp, $105.00.

Seyffart G, ed. *Drug Dosage in Renal Insufficiency*. Boston: Kluwer Academic Publishers, 1991, 650 pp, $225.00.

The Anesthesia and Critical Care Drugs Infobase, Version 1.0, Mount Vernon, Ill. Med-Pharm Systems Inc. On disk, $99.00.

Notice

ASA Members:

The ASA Task Force on Practice Parameters for Difficult Airway Management seeks input from anesthesiologists who will be attending the IARS Meeting in San Francisco. The Task Force is developing a set of practice guidelines for management of the patient with a difficult airway.

An open forum will be held at this meeting on March 14, 1992 from 1:30 PM to 5:00 PM. You are encouraged to review the practice guidelines at this forum and to comment publicly or by talking to individual members of the Task Force who will be present.

After the forum you are encouraged to provide written comments to: Robert A. Caplan, MD, Virginia Mason Medical Center, Department of Anesthesia, B2-AN, P. O. Box 900, Seattle, WA 98111. FAX Number (206) 223-6982.

Errata

Monk TG, Bouré B, White PF, Meretyk S, Clayman RV. Comparison of intravenous sedative-analgesic techniques for outpatient immersion lithotripsy. Vol. 72, No. 5, May 1991, p. 619.

The data points in Figure 1B were incorrectly labeled. A correct version of the figure is given below.

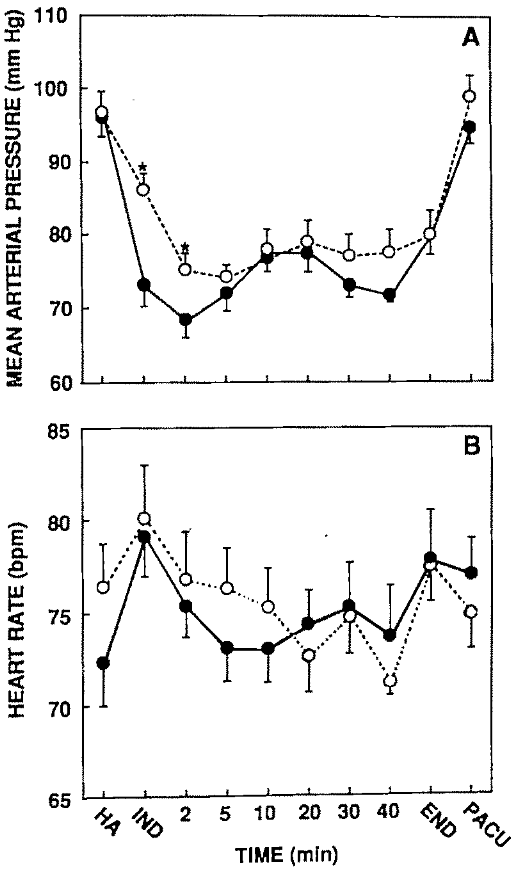

Figure 1. A, Perioperative mean arterial blood pressures in patients receiving either fentanyl-propofol (FP), $n = 26$ (—O—), or midazolam-alfentanil (MA), $n = 27$ (—●—). B, Heart rate values in patients receiving either fentanyl-propofol (FP), $n = 26$ (—O—) or midazolam-alfentanil (MA), $n = 27$ (—●—). Mean values ± SEM, $^*P < 0.05$ was considered to be statistically significant. HA, in preoperative holding area; IND, after the loading dose; END, at end of the ESWL procedure; PACU, in postanesthesia care unit.

Beebe DS, Belani KG, Mergens P, Liao J-C, So SKS, Najarian JS, Palahniuk RJ. Anesthetic management of infants receiving an adult kidney transplant. Vol. 73, No. 6, December 1991, p. 728.

Table 4, first column, fifth entry should read "Creatinine" not "Chromium."

The Origins of the Association of University Anesthesiologists

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William K. Hamilton, MD
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It is understandable as an evolutionary phenomenon that men band together—to form groups that can promote or defend more effectively than could be accomplished as individuals. It may also be a logical extension of this evolutionary process for them to split again from earlier and larger groups to focus more finely on special interests. Organized medicine and its continuing splintering and subspecialization is an example of this continuing evolutionary pattern. Dr. E. M. Papper (1) reports this historical practice in microcosm in the pleasant recounting of the conception, gestation, and birth of the Association of University Anesthesiologists (AUA).

A story of four concerned men who battled for cause is told to us in "The Origins of the Association of University Anesthesiologists." The triggering cause is perceived oppression of university anesthesiologists by the private sector of the specialty. The subject in question was "how physicians should be paid for their professional services with special emphasis on institutional salaries."

Why did this group of four feel so strongly the need to separate from the main organization, American Society of Anesthesiologists (ASA), which itself was only recently formed to further the causes of the young and growing specialty? Why did a separate association appear so desirable to them? Was the motivating drive really one of personal ego? Was it arrogance? Was it elitism in a university community that preferred to deal only with "higher" matters such as research and wanted to be a more select and prestigious organization? Could it not be argued that the policies of the ASA, which the new group abhorred, could be better dealt with from within the ASA than as a fledgling group on the outside? These questions seem even more interesting as the developing history indicates that the specific inciting cause disappeared from the AUA agenda immediately.

Of course, no answer is possible, but history will support that the main driving force resulting in the creation of the AUA must have been more than the payment issue. This subsequent history reveals further division even within the academic group. Very soon after the AUA was functioning, a group from the southeastern United States formed their own group of university Anesthesia Department Chairs and convinced the rest of the country that a nationwide Society of Academic Anesthesia Chairmen would be of benefit. Ostensibly, this group would deal only with administrative matters—those items worthy only of chairs' talents—above the interests and abilities of ordinary faculty. There is now a separate Program Directors group to bring the virtues of organization to non-university-based residency training program departments, which had been specifically and vigorously excluded from the Society of Academic Anesthesia Chairmen.

The divide and subdivide course of anesthesia parallels a course of almost all specialties in medicine. Division has occurred along many lines of special interests be it administration, subspecialty practice, research, type of practice, etc. The organizations are of course matched with new journals and new meetings and new trappings of membership and officialdom. This again suggests that something other than a specific cause was the genesis of the AUA and similar societies. The cause served as a focal point to bring the founding four together and to spur them to action. However, it seems likely that such a group wanted and needed to be formed for whatever cause. The pay issue was never a major item of action or agenda of the AUA, and its solution was well underway before the AUA was actually functioning.

There are interesting memories surfaced by Dr. Papper's treatise. Those of us born and reared in the Midwest and West will recognize at least some cause for our paranoia relative to the eastern seaboard. Philadelphia, Boston, and New York were the locations of the founding four. This can easily be expected by the demographics and history of our country at that time. However, the preference (Papper excepted) for a *very* small group, definition of the

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eastern seaboard as a membership qualification, and suggestion of *specific* exclusion of some departments from the Midwest and West with early inclusion of eastern departments without remarkable research activities is of interest as one explores motivations of the founders.

Another item of interest disclosed in this story is the degree of foment exhibited by Henry K. Beecher. This man's scholarship and contributions to the specialty are remarkable. His role in developing our research discipline is perhaps unequaled. However, he had then and much later a continuing adversity to the ASA and the American Board of Anesthesiology. His famous "curare death study" was an important part of the agenda at the January 1955 meeting of the AUA, and much discussion was critically pointed to the fact that Beecher published this in a surgical journal and reported it at a national surgical meeting, actually shunning his peers in anesthesia. He steadfastly refused to participate in the activities of the American Board of Anesthesiology. Thus the pay issue was not his only argument with the specialty, and the formation of the AUA did not alleviate his unhappiness with "the establishment." Of more interest than value is the recollection of minor developmental events not mentioned by Dr. Papper. AUA meetings were first held in January to minimize conflict with the busy national calendar. However, fate was against this idea. January is a good month to meet, but a bad month to travel. This was especially true in those times of less dependable air travel. There was even heavy snow in Durham, North Carolina in January of 1955. Subzero cold and wind chilled the group in Rochester and Minneapolis in January of 1956. Torrential downpours greeted us in New Orleans, Louisiana and Augusta, Georgia at later meetings, and thus the meetings dates were changed. The Association originally met in hospital and medical school facilities to actually view departments in their home environment. Whether because of size or unwillingness to meet in such spartan surroundings, the meetings soon moved to more comfortable surroundings.

What has been the effect of formation of the AUA? Dr. Papper informs us that the AMA never really implemented the dreaded Hess report and replaced it with a more tempered action. The American Board of Anesthesiology eliminated many of its restrictions for certification by 1953. The ASA and AUA have seldom if ever been in conflict and have evolved a symbiotic relationship in which the ASA has emerged as very helpful to the university community.

The feared exploitation of university faculties by university hospitals and similar institutions did not grow. As a matter of fact, university hospitals were to some extent at considerable disadvantage because of the shortage of academic anesthesiologists. Did the ASA stand help the specialty in this position? Was the ASA position stronger because of the cooperation that developed from the AUA? Would these good things have happened without the formation of the AUA? Were the actions of the founding four important in attenuating restrictive actions of organized medicine?

Has the AUA proved to be the voice of academe in our specialty? Have advances or improvements in our function as teachers, researchers, clinicians, or administrators been enhanced because of the AUA? The AUA has certainly been a pleasing and entertaining gathering for each of its years—is this its greatest achievement? If so, is this necessarily bad? Solid answers are missing but most of us would agree we benefitted from shared experiences and opinions. For this we are now and forever indebted to the founders. We are especially thankful that the sole surviving member of the founding four has presented this precious parcel of our history.

Reference

1. Papper EM. The origins of the Association of University Anesthesiologists. Anesth Analg 1992;74:436–53.

Anesthesiology and the Discipline of Medical Ethics: Challenges and Opportunities

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Conflicts resulting from rapidly advancing technology, economic constraints, shifting demographics, the medico-legal climate, and the heterogeneity of mores within our society have led to an abundance of ethical dilemmas involving health care delivery during the last several years (1). This seemingly exponential increase in medical ethics concerns has been reflected in a voluminous literature in the lay and medical press and the acceptance of "Medical Ethics" as a discipline in the sphere of academic medicine.

Coincidentally, anesthesiology has experienced a parallel and concurrent meteoric increase in the ranks of clinical medicine and academics. With its progressive involvement and leadership in areas such as critical care medicine and palliative care (i.e., pain management), the anesthesia literature has been remarkably barren of contributions pertaining to ethical quandaries. This silence was broken by Martin et al.'s (2) discussion of "Do Not Resuscitate" (DNR) orders in this journal, which was recently preceded by the article authored by Truog (3) in *Anesthesiology*. They elaborate and help to clarify the oftentimes murky and potentially disquieting issues that can arise while caring for patients who are high-risk surgical candidates with this advanced directive. They point out the important role that the anesthesiologist must serve in preoperative planning and counseling for patients (or their representatives) who have such directives. These contributions were certainly timely and helpful in their particular content. Moreover, they serve to point out one of the many seemingly hidden, yet immeasureably important, issues that routinely confront anesthesiologists. The context in which we practice medicine is as relevant as the medical expertise that we have to offer. This is what society is telling us. How do we take responsibility for this charge (4)? What makes the practice of anesthesiology unique in this way as a medical specialty?

General codes of conduct for physicians and even a specific ethical code that guides the professional actions and relationships of anesthesiologists are embodied, for instance, in The Hippocratic Oath, The World Medical Association Declaration of Geneva, The American Medical Association Principles of Medical Ethics, and The American Society of Anesthesiologists Guidelines for the Ethical Practice of Anesthesiology. These works, although punctuated with the flavor of their own particular historical origins, serve as the formal response to the need for a "universal" ethic. In sum, they assign the physician (anesthesiologist) a set of "behavioral" standards and help to define what that generally means. They do not direct the physician to challenge his or her own values (vis-à-vis those of the patient), and they do not charge the physician with formalizing his or her professional training with a structured means of recognizing, exploring, and resolving ethical dilemmas when they arise.

The practice of anesthesiology is virtually always a team effort. Although the "captain of the ship" doctrine has some historical legal force and some practical value when rapid, critical decisions are required, there is no real ethical basis for this (traditional) assignment of hierarchical responsibility between, say, surgeons and anesthesiologists (5). Using the surgeon-anesthesiologist paradigm, if the anesthesiologist knowingly or unconsciously yields moral authority during any phase of a case to the surgeon, he or she has ceased to be a physician in the whole sense (6) and has not maintained his or her implicit contract with the patient. Perhaps there are circumstances that warrant this, but as an a priori "given," this requires some exploration. I submit that, based on the published literature, there is little guidance to be had in the form of conscious recognition and purposeful reconciliation of the difficulties inherent in this relationship (the "physician–patient relationship"). This type of conflict has been referred to in other areas of health care as the "Ethics of Interdependence" (7). A more palatable and practical terminology apropos to anesthesia practice might be the "responsibilities of shared care."

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The DNR scenarios elaborated by Martin et al. (2) represent one of many potentially difficult situations encountered by anesthesiologists in all types of practice. For example, how does the anesthesiologist become involved in the informed consent process leading to an operative delivery of a probably unsalvageable neonate? The desire to get along and a spirit of cooperation are laudable characteristics and may help to keep strife at bay. However, and more realistically, as various members of the "care team" become more sensitive to ethical issues and the more assertive the public becomes in their demands for consideration of their values and autonomy, the necessity for constructive approaches to conflict resolution will become obvious, if, indeed, it already hasn't. Denial, avoidance, hidden resentment, and shifting of blame are reflexive but seldom productive defenses against controversy and change. I propose that a proactive course would best serve to support the professionalism, integrity, and leadership that our specialty has worked for in so many other domains. Indeed, the roots of such thinking reach deeply into our professional origins.

We can discover one source by returning to the focal article of this editorial. Martin et al. (2) begin their paper with a quotation from Wesley Bourne's "On the Duties of the Anaesthesiologist as a Physician" (8). These authors' choice of whom to quote is quite poignant and appropriate in the present context. Bourne says that "The patient is not a problem; he is a person with a problem." He attributes goodness in a physician to that quality described in Immanuel Kant's second maxim: "Act so as to treat humanity, whether in thine own person or in the person of another, always as an end, never as a means only." Bourne goes on to draw upon the now famous statement of Francis Peabody while addressing Harvard medical students: "One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring *for* the patient." Of significance, Wesley Bourne, MD, a Canadian, was president of the International Anesthesia Research Society for two terms (1925 and 1940) and served as the only non-American president of the American Society of Anesthesiologists. So, with all of this philosophy and history setting the stage, how do we actually move toward that lofty place to which we are directed?

First, just as there is not yet a single, perfect anesthetic technique, it must be acknowledged that no one has a corner on the market for "morality" or "ethical rightness." Then, just as we arm ourselves with well-constructed arguments (based on the "known," the "probable," and the "unknown") for choosing a specific anesthetic technique in a difficult clinical situation, a similar approach is needed in facing clinical ethical dilemmas. This requires a fund of knowledge and a structured approach to sorting out the issues. Armed with these tools, then one might consider oneself to be both responsible and entitled to an opinion. It is time, now, to integrate such material into residency training and our professional society meetings while taking some personal responsibility for informing ourselves. We can then be prepared to address cases that come to the fore in a rigorous manner—and we need to do so, honing our skills on a regular basis, in all practice settings. It would be a good beginning.

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Comparative Hemodynamic Depression of Halothane Versus Isoflurane in Neonates and Infants: An Echocardiographic Study

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The purpose of this study was to measure and compare the relationship of cardiovascular depression and dose during equal potent levels of halothane and isoflurane anesthesia in neonates ($n = 19$) (16.7 ± 6.9 days) and infants ($n = 54$) (6.1 ± 3.1 mo). Seventy-three children had heart rate, arterial blood pressure, and pulsed Doppler pulmonary blood flow velocity as well as two-dimensional echocardiographic assessments of left ventricular area and length recorded just before anesthesia induction. Anesthesia was induced by inhalation of increasing inspired concentrations of halothane or isoflurane in oxygen using a pediatric circle system and mask. During controlled ventilation, halothane and isoflurane concentrations were adjusted to maintain 1.0 MAC and then 1.5 MAC (corrected for age), and echocardiographic and hemodynamic measurements were repeated. A final cardiovascular measurement was recorded after intravenous administration of 0.02 mg/kg of atropine. All measurements were completed before tracheal intubation and the start of elective surgery. In neonates, 1.0 MAC concentrations of halothane and isoflurane decreased cardiac output (74% ± 16%), stroke volume (75% ± 15%), and ejection fraction (76% ± 15%) similarly from awake levels. Decreases in cardiac output, stroke volume, and ejection fraction with halothane and isoflurane were significantly larger at 1.5 MAC (~35% decreases from awake values) than at 1.0 MAC. Heart rate decreased significantly during 1.5 MAC halothane anesthesia (94% ± 4%) but remained unchanged during isoflurane anesthesia. In infants, 1.0 MAC halothane and isoflurane decreased cardiac output (83% ± 12%), stroke volume (78% ± 12%), and ejection fraction (74% ± 12%) when compared with awake measures. Heart rate decreased during 1.0 MAC halothane anesthesia but increased during 1.0 MAC isoflurane. When anesthetic concentrations were increased to 1.5 MAC, stroke volume (71% ± 12% of awake) and ejection fraction (64% ± 13% of awake) decreased similarly from the 1.0 MAC measurement in both groups. When compared with 1.0 MAC, heart rate decreased further at 1.5 MAC halothane anesthesia (80% ± 5% of awake) but remained unchanged during 1.5 MAC isoflurane anesthesia (106% ± 4% of awake). Atropine (0.02 mg/kg) increased heart rate and cardiac output by 15%–20% from measurements at 1.5 MAC halothane and isoflurane anesthesia in neonates and infants, but stroke volume and ejection fraction remained unchanged from measurements before atropine administration in both groups. Equipotent halothane and isoflurane produced similar hemodynamic depression in neonates and infants.

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Comparative in vitro and in vivo cardiovascular studies in young versus older animals indicate that the immature, developing cardiovascular system is more sensitive to depression by inhaled anesthetics (1–5). Cardiovascular sensitivity is cited as a contributing factor to a higher incidence of anesthesia-related human cardiac arrests during infancy (6–8). The increased incidence of bradycardia, hypotension, and cardiac arrest in infants less than 12 mo of age when compared with adults suggests hemodynamic sensitivity to inhaled anesthetics extends from birth throughout the first year (6–11). Neonates are believed to be the most susceptible to hemodynamic depression from inhaled anesthetics, but major surgery during the neonatal period may also contribute to the increased incidence of anesthesia-related complications (11).

Most clinical studies in pediatric patients that report greater hemodynamic sensitivity are based on cardiovascular measures at stable inspired halothane or isoflurane concentrations rather than end-tidal concentrations (12–14). The purported sensitivity of

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neonates and infants to inhaled anesthetics may be a function of uptake and distribution differences rather than greater susceptibility to myocardial depression (15). When equal *inspired* concentrations of halothane and isoflurane are administered, higher partial pressures of volatile anesthetics in brain and myocardium are more rapidly achieved in neonates and infants than adults because of a relatively larger vessel-rich tissue group and lower volatile anesthetic tissue solubility in the young compared with the adult (15,16).

In neonates and infants, heart rate and systolic blood pressure measurements at 1.0 MAC halothane anesthesia do not confirm speculations of increased hemodynamic sensitivity (17). When additional cardiovascular determinants have been measured during equal MAC halothane or isoflurane administration, the study population included older infants and small children (mean age = 12 mo) (18). The purpose of this study was to obtain dose-response measures of hemodynamic depression and to compare the cardiovascular changes at equipotent (equal MAC) concentrations of halothane versus isoflurane in separate groups of healthy neonates (<28 days) and infants (<1 yr of age).

Methods

Seventy-three ASA physical status I neonates ($n = 19$) and infants ($n = 54$) who required elective surgery were studied after the protocol was approved by the Human Studies Committee. Informed written parental consent was obtained. The neonates (mean age, 16.6 ± 6 days; mean weight, 3.2 ± 4 kg) and infants (mean age, 6.1 ± 2.4 mo; mean weight, 7.4 ± 1.5 kg) received no anesthetic premedicants and were NPO for 4 h preoperatively. All neonates and infants included in the study were 38 wk or more by gestational assessment at birth and had no neurologic, respiratory, or cardiovascular diseases. The planned neonatal operations included cataract extraction ($n = 7$), urologic procedures ($n = 5$), and lower abdominal surgery ($n = 7$). Operations in infants included inguinal herniorrhaphy ($n = 11$), orthopedic procedures ($n = 11$), urologic operations ($n = 16$), and cleft lip or palate repairs ($n = 16$).

Parents accompanied their children to a preanesthetic care unit where baseline cardiovascular data were recorded. Heart rate by electrocardiogram monitoring, blood pressure by automated oscillotonometry (Omega 1600) and pulsed Doppler and two-dimensional echocardiographic data (Hewlett-Packard Sonos 500) were collected at each study period. Echocardiographic data obtained in every patient included short axis views at the high left ventricular papillary muscle and great vessel level plus apical four-chamber views of the myocardium. After the heart and great arteries were imaged, Doppler flow velocities were obtained from the pulmonary artery immediately above the pulmonic valve. Sample volumes were positioned to measure maximal flow velocities. The audio signal intensity and Doppler shift frequency spectral displays were used to confirm positioning for maximal pulmonary artery blood flow velocities. Peak velocity was measured to the apex of the most dense signal on the velocity curve. Three beats were averaged. The Doppler profile was continuously updated using two-dimensional images. Simultaneous electrocardiographic tracings were displayed on a monitor and recorded on videotape. Selective frozen images were recorded on videotape for later analysis and measurement.

Neonates and infants were alternatively assigned to either halothane ($n = 38$) or isoflurane ($n = 35$) study groups after the baseline cardiovascular measurements. Using 3–5-L/min oxygen flow, anesthesia was induced with inspired increments of halothane or isoflurane administered via Rendell-Baker mask and pediatric circle system. The inspired isoflurane and halothane increments were 0.2%. If breathholding or coughing occurred during induction of anesthesia, the inspired anesthetic concentration was either decreased or held constant until a regular ventilatory pattern was reestablished. None of the patients required additional intervention to treat airway irritability. During inhaled induction of anesthesia, the maximum inspired concentrations of halothane and isoflurane administered were 2.0 and 3.0 vol%, respectively. Monitoring during anesthesia included precordial stethoscope, pulse oximetry, electrocardiogram, and automated noninvasive blood pressure (Omega 1600). After loss of consciousness, ventilation by mask was controlled with respiratory rates from 16–25 breaths/min. Anesthetic gas concentrations and carbon dioxide concentrations were measured from gas samples continuously aspirated (60 mL/min) from an elbow connector attached to the Rendell-Baker mask. Capnograms as well as inspired and expired gas concentrations (oxygen, nitrogen, halothane, and isoflurane) were recorded every minute using a printer interfaced with a Perkin Elmer mass spectrometer. End-expired concentrations of halothane and isoflurane were recorded when an alveolar plateau of greater than 0.2 s was achieved during the study period and a CO_2 waveform lasted longer than 0.6 s (19).

After anesthesia induction, inspired MAC anesthetic concentrations were adjusted to maintain end-expired concentrations at 1.0 MAC (adjusted for age) (17,20). When the inspired and expired concentrations of halothane and isoflurane had been stable for

Table 1. Anesthetic Concentrations in Neonates and Infants

	1.0 MAC (vol%)		1.5 MAC (vol%)	
Group	Expired	Inspired	Expired	Inspired
Neonates (n = 19)				
Halothane (n = 10)	0.89 ± 0.04	1.10 ± 0.09	1.32 ± 0.05	1.55 ± 0.10
Isoflurane (n = 9)	1.52 ± 0.18	1.86 ± 0.09	2.18 ± 0.13	2.54 ± 0.23
Infants (n = 54)				
Halothane (n = 28)	1.12 ± 0.08[a]	1.38 ± 0.14[a]	1.59 ± 0.18[a]	1.97 ± 0.25[a]
Isoflurane (n = 26)	1.77 ± 0.08[a]	2.10 ± 0.10[a]	2.59 ± 0.20[a]	3.14 ± 0.13[a]

Values are reported as mean ± SD. The inspired and expired halothane and isoflurane concentrations are higher in infants than neonates.
[a]Different from neonate values ($P < 0.01$).

10 min at the 1.0 MAC concentration (20 min after the induction of anesthesia), a second set of cardiovascular data was collected over a 2-min period. Anesthetic depth was then gradually increased to achieve end-expired concentrations of halothane or isoflurane equivalent to 1.5 MAC. When constant end-expired and inspired halothane or isoflurane concentrations had been recorded for 6 min (approximately 10 min after the 1.0 MAC measurement), a third set of cardiovascular data was collected over a 2-min period. After the measurement at 1.5 MAC, an intravenous dose of atropine (0.02 mg/kg IV) was administered and, 2 min later, a final cardiovascular measurement was made again at 1.5 MAC halothane or isoflurane anesthesia. Ventilation was controlled throughout the study period, intravenous fluids were withheld, and all cardiovascular measurements were completed before tracheal intubation and the start of elective surgery. The duration of the study period from start of anesthesia induction to study completion was 40 min.

The echocardiographic technician and pediatric cardiologist were blinded to the inhaled anesthetic used during the study. Videotaped recordings of pulsed Doppler and two-dimensional echocardiography were analyzed using a microsonic CAD-886 image processing and video quantifications system (Microsonics, Inc., Indianapolis, Ind.). Left ventricular endocardial enclosed volumes were measured separately at end-diastole and end-systole from two orthogonal planes: parasternal short axis and apical four-chamber views. Images were traced along the endocardium utilizing the leading edge method (21–23). Two-dimensional recordings of left ventricular area at papillary muscle level and left ventricular length at end-systole and end-diastole were used to calculate left ventricular end-systolic and left ventricular end-diastolic volumes at each study level (21–23). Volume was calculated as

$$\text{Volume} = \tfrac{5}{6}\ \text{Area} \times \text{Length}.$$

The Doppler-determined mean velocities of pulmonary artery blood flow and echocardiographically determined pulmonary artery diameters were used to calculate cardiac output. Cardiac output was determined as mean pulmonary blood flow velocity × pulmonary artery area (24–26).

All data are reported as mean ± SD and were analyzed using randomized block analysis of variance with factors being age (neonates and infants), anesthetic agents (halothane and isoflurane), and drug concentrations (awake, 1.0 MAC, and 1.5 MAC and 1.5 MAC with atropine). Bonferroni adjustments were made based on the multiple comparisons. Significance was accepted at $P < 0.05$. When significant interaction was present, follow-up comparisons were made and corrected using Duncan's procedure.

Results

Neonates

The mean age (13.7 ± 6 days), weight (3.1 ± 0.4 kg), and body surface area (0.22 ± 0.01 m^2) of neonates who received halothane (n = 10) was similar to the mean age (19.6 ± 7 days), weight (3.1 ± 0.2 kg), and body surface area (0.21 ± 0.01 m^2) of neonates who received isoflurane (n = 9).

The 1.0 MAC anesthetic concentration recorded during cardiovascular measurements was 0.89 ± 0.04 vol% during halothane and 1.52 ± 0.18 vol% during isoflurane (Table 1). The mean end-tidal CO_2 recorded during the study period was similar in both groups (29 ± 6 mm Hg). During the study period, end-expired CO_2 varied by a maximum of ± 6 mm Hg in individual patients from the mean end-expired CO_2 recorded during 1.0 MAC halothane or isoflurane.

At 1.0 MAC halothane and isoflurane in neonates, heart rate was unchanged from awake measurements (Table 2). Decreases in cardiac output (Figure 1), stroke volume (Figure 2), and percent change in

Table 2. Neonatal Cardiovascular Data

	Awake	1.0 MAC	1.5 MAC	1.5 MAC + atropine
HR (beats/min)				
Halothane	144.4 ± 15.6	143.1 ± 13.1	134.9 ± 16.9[a,b]	153.9 ± 10.4[a,b]
Isoflurane	154.4 ± 12.8	152.7 ± 29	154 ± 23.7	177.2 ± 17.3[a]
MBP (mm Hg)				
Halothane	58.8 ± 4.1	50.3 ± 3.4[a]	45.5 ± 3.9[a]	48.9 ± 3.8[a]
Isoflurane	67.0 ± 5.8	56.7 ± 7.1[a]	50.7 ± 7.0[a]	52.7 ± 9.7[a]
CI ($L \cdot min^{-1} \cdot m^{-2}$)				
Halothane	3.70 ± 1.15	2.71 ± 0.82[a]	2.17 ± 0.75[a]	2.62 ± 0.75[a]
Isoflurane	3.97 ± 1.14	2.92 ± 0.48[a]	2.72 ± 0.44[a]	3.50 ± 0.92[a]
SVI (mL/m^2)				
Halothane	26.0 ± 8.9	19.1 ± 6.4[a]	16.3 ± 4.9[a]	17.4 ± 5.6[a]
Isoflurane	25.8 ± 7.3	19.6 ± 4.1[a]	18.4 ± 5.9[a]	20.1 ± 5.3[a]
LVEDV (mL)				
Halothane	6.0 ± 1.9	5.9 ± 1.4	5.6 ± 1.4	5.8 ± 1.4
Isoflurane	7.1 ± 2.0	7.0 ± 1.4	7.0 ± 1.3	7.1 ± 1.3

HR, heart rate; MBP, mean arterial blood pressure; CI, cardiac index; SVI, stroke volume index; LVEDV, left ventricular end-diastolic volume. Results are expressed as mean ± SD.
[a] Different from awake values ($P < 0.05$).
[b] Different from isoflurane values ($P < 0.05$).

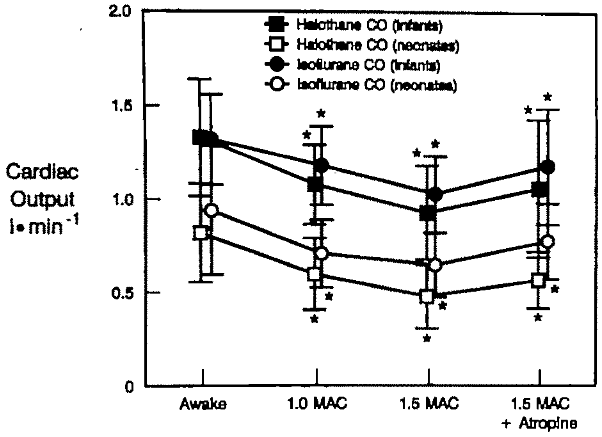

Figure 1. Cardiac output in neonates (□, halothane; ○, isoflurane) and infants (■, halothane; ●, isoflurane). Results are expressed as mean ± SD. *$P < 0.05$ from awake.

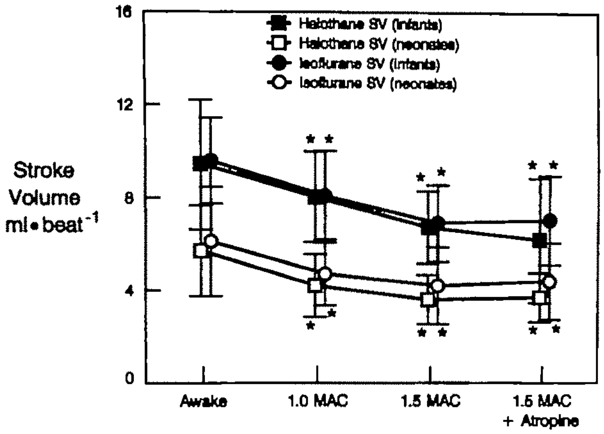

Figure 2. Stroke volume in neonates (□, halothane; ○, isoflurane) and infants (■, halothane; ●, isoflurane). Results are expressed as mean ± SD. *$P < 0.05$ from awake.

ejection fraction (Figure 3) and mean arterial blood pressure were also similar at 1.0 MAC halothane and isoflurane anesthesia. When cardiac output and stroke volume are indexed to body surface area, cardiac index and stroke volume index decreased similarly at 1.0 MAC halothane and isoflurane (Table 2). Left ventricular end-diastolic volume was unchanged during the study period (Table 2).

When anesthetic concentrations were increased to 1.5 MAC halothane and isoflurane in neonates, stroke volume and ejection fraction decreased further (Figures 2 and 3). Heart rate decreased during 1.5 MAC halothane but remained unchanged during isoflurane anesthesia. Cardiac output and stroke volume decreased to 59% ± 21% and 63% ± 21% of awake measurements with 1.5 MAC halothane concentration (Figures 1 and 2). During 1.5 MAC isoflurane, cardiac output and stroke volume were 70% ± 24% and 69% ± 21% of awake values, respectively (Figures 1 and 2). Ejection fractions declined to 65% ± 16% and 68% ± 14% of awake values during 1.5 MAC halothane and isoflurane, respectively (Figure 3). Cardiac output, stroke volume, and ejection fraction declined similarly during equal MAC halothane and isoflurane anesthesia.

Atropine increased heart rate, cardiac index (Table 2), and cardiac output (Figure 1). The increase in heart rate and cardiac output after atropine was

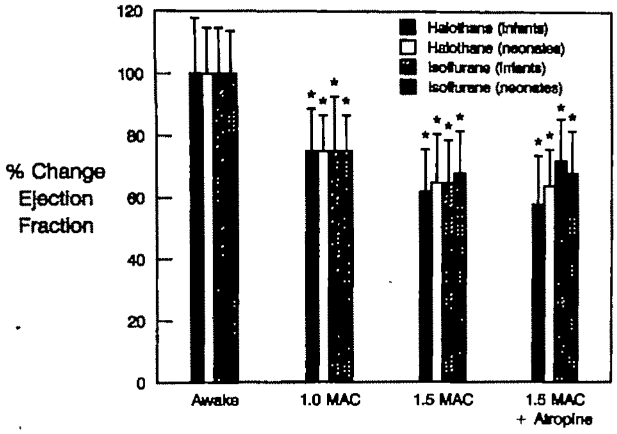

Figure 3. Percentage of control ejection fraction in neonates and infants during halothane and isoflurane anesthesia. Results are expressed as mean ± SD. $^*P < 0.05$ from awake.

similar in both halothane and isoflurane groups (Table 2). Stroke volumes (Figure 2) and ejection fractions (Figure 3) were unchanged after intravenous atropine. Although cardiac output increased after atropine, cardiac output remained depressed from awake values (Figure 1). Mean blood pressure and left ventricular end-diastolic volume also remained unchanged after atropine (Table 2).

Infants

The mean age (6.3 ± 3.5 mo), weight (7.4 ± 2.0 kg), and body surface area (0.40 ± 0.04 m^2) of infants who received halothane was similar to the mean age (5.9 ± 3.1), weight (7.4 ± 1.5 kg), and body surface area (0.38 ± 0.04 m^2) of infants who received isoflurane anesthesia. At the time of the cardiovascular measurements, end-expired halothane concentrations were 1.12 ± 0.08 vol% and 1.59 ± 0.18 vol% with 1.0 and 1.5 MAC, respectively (Table 1). Expired isoflurane concentrations recorded at 1.0 MAC and 1.5 MAC were 1.77 ± 0.08 vol% and 2.59 ± 0.20 vol%, respectively (Table 1). The ratio between expired and inspired concentrations of halothane and isoflurane at the time of the cardiovascular measurements was similar for halothane and isoflurane. The mean expired CO_2 measured during the study period was 32.2 ± 4.1 mm Hg. In each patient, variation in expired CO_2 during the entire study period was ±4 mm CO_2.

The awake cardiovascular measurements of heart rate, mean blood pressure, cardiac output, stroke volume, and left ventricular end-diastolic volume were similar in both infant groups (Table 3). During halothane anesthesia, heart rate decreased in a dose-related manner to 93% ± 5% and 85% ± 5% of awake at 1.0 MAC and 1.5 MAC, respectively (Table 3). During isoflurane anesthesia, heart rate increased similarly at 1.0 and 1.5 MAC concentrations (106% ± 7% of awake) (Table 3). Although halothane and isoflurane had different effects on heart rate, there were no other hemodynamic differences between equal MAC concentrations of the two volatile anesthetics. When cardiac output and stroke volume were indexed to body surface area, cardiac index and stroke volume index (Table 3) decreased similarly during halothane and isoflurane anesthesia (83% ± 12% of awake) at 1.0 MAC and (74% ± 15% of awake) at 1.5 MAC.

Mean blood pressure and stroke volume index decreased further when concentrations of halothane and isoflurane anesthesia were increased to 1.5 MAC (Table 3). Stroke volumes and ejection fraction decreased similarly during halothane and isoflurane anesthesia (Figures 2 and 3). During 1.5 MAC halothane, stroke volume and ejection fraction decreased to 70% ± 15% and 62% ± 16% of awake values, respectively (Figures 2 and 3). Stroke volume and ejection fraction decreased to 72% ± 15% and 65% ± 14% of awake values, respectively, at 1.5 MAC isoflurane (Figures 2 and 3). The 1.0 and 1.5 MAC halothane and isoflurane concentrations increased left ventricular end-systolic and end-diastolic volumes similarly in both groups.

After atropine (0.02 mg/kg) administration, cardiac output increased similarly during halothane and isoflurane anesthesia (Figure 1). Heart rate increased after atropine. In infants maintained at 1.5 MAC concentrations of halothane, heart rate increased (27% ± 8%) more than during isoflurane anesthesia (12% ± 5%) (Table 3). Stroke volume and ejection fraction were unchanged from values recorded at 1.5 MAC (Figures 2 and 3). The increased heart rate after atropine was higher than awake heart rates in both groups (Table 3).

Neonates Versus Infants

The expired and inspired halothane and isoflurane concentrations required in infants to achieve 1.0 and 1.5 MAC were significantly higher than in neonates (Table 1). Equal MAC halothane and isoflurane concentration led to similar decreases in cardiac output, blood pressure, stroke volume, and ejection fraction in neonates and infants. When cardiac output and stroke volume were indexed to body surface area, cardiac index and stroke volume index decreased similarly in neonates and infants (Tables 2 and 3). The only hemodynamic differences between neonates and infants at equal anesthetic concentrations of halothane or isoflurane were changes in heart rate and left ventricular end-diastolic volume. Heart rate decreased more in infants than neonates during halothane anesthesia. At 1.5 MAC halothane, heart

Table 3. Infant (1–12 mo) Cardiovascular Data

	Awake	1.0 MAC	1.5 MAC	1.5 MAC + atropine
HR (beats/min)				
Halothane	139 ± 19	129 ± 15[a,b]	120 ± 17[a,b]	154 ± 18[a,b]
Isoflurane	139 ± 13	148 ± 18[a]	151 ± 16[a]	169 ± 17[a]
MBP (mm Hg)				
Halothane	73.4 ± 5.2	62.2 ± 6.2[a]	53.7 ± 4.9[a]	58.2 ± 8.3[a]
Isoflurane	73.8 ± 6.5	64.8 ± 9.6[a]	57.6 ± 8.0[a]	56.9 ± 10.2[a]
CI ($L \cdot min^{-1} \cdot m^{-2}$)				
Halothane	3.35 ± 0.89	2.72 ± 0.69[a]	2.36 ± 0.61[a]	2.16 ± 0.59[a]
Isoflurane	3.15 ± 0.54	2.84 ± 0.49[a]	2.45 ± 0.36[a]	2.82 ± 0.49[a]
SVI (mL/m^2)				
Halothane	23.3 ± 5.8	19.9 ± 5.1[a]	17.5 ± 4.5[a]	15.5 ± 5.6[a]
Isoflurane	22.7 ± 3.3	19.3 ± 3.7[a]	16.9 ± 2.8[a]	16.8 ± 2.7[a]
LVEDV (mL)				
Halothane	11.8 ± 3.3	13.5 ± 3.1[a]	14.1 ± 3.8[a]	13.9 ± 3.3[a]
Isoflurane	12.7 ± 4.1	13.0 ± 4.0	14.1 ± 4.1[a]	14.5 ± 4.4[a]

HR, heart rate; MBP, mean arterial blood pressure; CI, cardiac index; SVI, stroke volume index; LVEDV, left ventricular end-diastolic volume.
Results are expressed as mean ± SD.
[a] Different from awake values ($P < 0.05$).
[b] Different from isoflurane values ($P < 0.05$).

rate decreased to 85% ± 10% of awake in infants, whereas in neonates at 1.5 MAC halothane, heart rate decreased to 94% ± 6% of awake. Isoflurane increased heart rate in infants (106% ± 6% of awake) but not in neonates. The mean increase in heart rate (20%) after atropine was similar in neonates and infants, but in infants who received halothane, heart rate increased 27% ± 6%, whereas during isoflurane anesthesia the increase in heart rate was 12% ± 6%. Left ventricular end-diastolic volume increased in infants but was unchanged in neonates (Tables 2 and 3).

Discussion

In neonates, the similar changes in cardiac output, stroke volume, ejection fraction, and end-diastolic volume suggest that contractility and preload are similarly affected during equal MAC halothane and isoflurane anesthesia. The similar effect of the two anesthetics on mean arterial blood pressure and left ventricular end-systolic volume indicates peripheral vascular changes are also similar during equal MAC halothane and isoflurane anesthesia. Mean arterial blood pressure and heart rate changes in this study were similar to findings of Lerman et al. (17) and LeDez and Lerman (27) when the MAC of halothane and isoflurane was determined in neonates and premature infants, respectively. In an in vitro study that assessed contractility of newborn and young rabbit myocardia, Murat et al. (3) compared approximately equal anesthetic concentrations of halothane and isoflurane and found similar decreases in contractility with halothane and isoflurane. In newborn piglets, Boudreaux et al. (4) and Scheiber et al. (5) reported similar decreases in myocardial contractility with approximately equally potent halothane and isoflurane concentrations, but isoflurane maintained cardiac output because of a decrease in afterload.

In infants, the major cardiovascular difference between equal MAC halothane and isoflurane was heart rate. An increased heart rate during isoflurane may indicate better preservation of sympathetic activity with isoflurane than with halothane. Alternatively, baroreceptor function may be maintained during isoflurane but not halothane anesthesia (28,29). As in the neonates, the similar changes in left ventricular end-diastolic volume, mean arterial blood pressure, ejection fraction, cardiac output, and stroke volume indicate equal MAC halothane and isoflurane must have similar effects on contractility and preload in infants. Overall peripheral vascular changes in infants must also be similar with halothane and isoflurane. In adults, isoflurane, in contrast to halothane, markedly increased muscle blood flow leading to net decreased peripheral resistance (28,29). The relatively smaller muscle mass and larger vessel-rich group in infants may lead to similar overall changes in blood flow to organ systems, and the net change in vascular resistance with halothane and isoflurane appears similar in infants (18). This hypothesis would need to be confirmed using a better assessment of peripheral vascular changes in infants and children.

Heart rate and left ventricular end-diastolic volume were different in neonates and infants at equal MAC halothane and isoflurane anesthesia. The absence of heart rate changes in neonates compared with infants may be a manifestation of lesser autonomic regulation of heart rate in neonates, or perhaps the lower end-tidal anesthetic concentrations in neonates compared with infants caused less effect on cardiac rate. The absence of changes in left ventricular end-diastolic volume in neonates compared with infants may represent a different effect of volatile anesthetics on preload in the neonate, a difference in myocardial compliance between neonates and infants, or perhaps a greater hemodynamic effect of controlled ventilation in neonates. The use of controlled ventilation with large tidal volumes (end-tidal CO_2, 30 ± 4 mm Hg) by impairing venous return might lead to decreases in left ventricular end-diastolic volume and a greater decrease in cardiac output and stroke volume in neonates and infants than in adults or older children (18).

Differences in volatile anesthetic pharmacology between neonates, infants, and adults were not considered in clinical studies that contend greater hemodynamic sensitivity in pediatric patients (9,10,12–14). Brandom et al. (15) predicted and observed higher end-tidal concentrations of anesthesia at equal inspired concentrations when vessel-rich tissue equilibrium had been achieved in infants compared with adults. They concluded that cardiovascular data collected in pediatric patients based on inspired halothane and isoflurane concentrations rather than end-tidal concentrations may be misinterpreted as indicating heightened cardiovascular sensitivity in the child. In prior pediatric clinical studies, the conclusion of greater hemodynamic sensitivity in children compared with adults has been based on cardiovascular measurements recorded during stable inspired anesthetic concentrations (9,10,12–14). Nitrous oxide and premedication were also administered (9,10,12–14). We measured hemodynamic data at constant end-expired halothane and isoflurane concentrations without nitrous oxide or premedication. The inspired halothane and isoflurane concentrations required to achieve 1.5 MAC end-expired concentrations in this study were lower than inspired concentrations used in prior studies of infants and children (9,10,14).

In animal studies, conclusions of inhaled anesthetic hemodynamic susceptibility of the young compared with the older animal have been based on cardiovascular comparisons at equal tissue concentrations (1–5) rather than equal MAC concentrations. We found similar hemodynamic depression at equal MAC in neonates and infants, but because of the lower neonatal MAC, significantly lower end-tidal concentrations were used in neonates than infants. This difference suggests neonates may be more sensitive to inhaled anesthetic-induced hemodynamic depression than infants and perhaps adults. Developmental changes in the troponin and tropomyosin complex after birth may be responsible for this difference. Murat et al. (3) found halothane and isoflurane decreased Ca^{2+} sensitivity and contractility of skinned rabbit myocardial muscle until 20 days of life. If hemodynamic sensitivity occurred in the infants, we anticipated stroke volume and cardiac output decreases would be larger in prior studies of older infants and children than reported in healthy adult volunteers at similar end-tidal concentrations (18,28,29). While a comparative study at equal halothane and isoflurane tissue concentrations in infants and adults is required, greater cardiovascular depression observed in infants when compared with prior studies of adults appears primarily related to increased inhaled anesthetic requirements and uptake and distribution differences rather than hemodynamic sensitivity.

Similar to prior studies in infants and small children, the increased heart rate after atropine increased cardiac output but did not attenuate myocardial depression as measured by ejection fraction and stroke volume in either neonates or infants (30). The increased heart rate did not compensate for decreased stroke volume, and cardiac output remained depressed from awake levels in both neonates and infants.

The noninvasive two-dimensional and pulsed Doppler echocardiographic measurement technique used to determine left ventricular short axis area and length and pulmonary artery flow velocity in neonates and infants makes assumptions when left ventricular volume and cardiac output are calculated. Left ventricular volumes obtained by two-dimensional echocardiography underestimate angiographic volumes. Cardiac output determination is affected by both the accuracy of pulmonary artery area measurement and mean pulmonary artery flow velocity measurement. The Doppler sending and receiving probe must be placed similarly during each measurement. The accuracy of blood flow velocity measures can be affected if the angle of incidence of the Doppler signal with pulmonary blood flow varies during repeated measures. When pulsed Doppler and two-dimensional data are obtained by a trained echocardiographic technician and calculated using standardized echocardiographic measurements, correlation coefficients of cardiac output and left ventricular volumes with angiographic measures in infants and children with normal and abnormal cardiovascular systems are greater than 0.9 (21–26).

The precision of expired gas concentration measurements is limited if inspired gas is entrained during the study period (31–33). End-tidal CO_2 measurements would be altered more than expired halothane or isoflurane concentrations by the entrainment of inspired gas. We used controlled ventilation, a pediatric circle system, and respiratory rates lower than 30 breaths/min to improve separation of inspired from expired gases (31,32). If expired gases were contaminated with the higher inspired halothane or isoflurane concentrations, end-tidal concentrations would be overestimated and an underestimate of cardiovascular changes during halothane and isoflurane anesthesia would result. Tracheal gas samples obtained from the distal end of a tracheal tube would have improved the accuracy of end-expired gas measurements (31,32), but the administration of atropine before intubation and hemodynamic changes from tracheal intubation would likely have affected cardiovascular interpretation (12,14,30).

Alveolar anesthetic concentrations approach vessel-rich anesthetic concentrations over time (34). End-expired concentrations were maintained constant for three predicted vessel-rich time constants in neonates and infants before the hemodynamic measurements (15). Three predicted time constants should assure that end-tidal anesthetic concentrations were 95% of anesthetic partial pressures in the central nervous system (34).

In summary, equipotent halothane and isoflurane concentrations in neonates and infants decrease cardiac output, stroke volume, and ejection fraction similarly. The cardiovascular depression is dose-related with decreases of more than 30% in ejection fraction and stroke volume at 1.5 MAC concentrations. The primary cardiovascular difference between halothane and isoflurane is a differing effect on heart rate. Hemodynamic depression is greater in neonates and infants than reported in prior studies of small children and adults at equivalent age-corrected MAC concentrations. Because end-tidal concentrations in neonates were significantly lower than in infants, neonates may be more susceptible to inhaled anesthetic-induced hemodynamic depression than infants. In infants, the observation of greater hemodynamic depression during inhalation anesthesia is primarily due to uptake and distribution differences and increased anesthetic requirements rather than heightened cardiovascular susceptibility to inhaled anesthetics.

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Differential Sensitivity to Halothane Anesthesia of the Genioglossus, Intercostals, and Diaphragm in Kittens

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Recent studies in humans and animals have indicated that different inspiratory muscles have different sensitivities to respiratory depressants. The sensitivity of inspiratory muscles during early growth and development relative to that in adults of the same species, however, has not been studied. We therefore studied the activity of the diaphragm, the external intercostals, and the genioglossus by means of electromyography and its moving time average with different concentrations of halothane in seven 2-mo-old kittens. The kittens spontaneously breathed 1.0%–2.0% halothane in oxygen while $Paco_2$ was maintained at about 60 mm Hg by adding CO_2 to the inspired gas as needed. Muscle activity was evaluated in terms of the peak height of the moving time average. Activity at 1% halothane was used as the control measurement because measurements at zero inspired concentrations of halothane could not be obtained without sedation, which is known to depress respiratory muscle activity. Halothane anesthesia significantly ($P < 0.01$) decreased phasic inspiratory activity of the inspiratory muscles in a dose-dependent fashion. Genioglossal activity was completely abolished at 1.5% and 2.0% halothane. By contrast, in our previous study in adult cats under nearly identical experimental conditions, the phasic genioglossal activity was depressed but present even at 3.0% halothane. The degree of depression at 1.5% and 2.0% halothane was least in the crural diaphragm (71.8% ± 5.8%, 66.6% ± 4.5% of control, respectively), intermediate in the intercostals (68.9% ± 9.6%, 35.4% ± 8.8%), and greatest in the genioglossus (0.0%, 0.0%). Respiratory frequency, inspiratory time, and inspiratory duty cycle did not change significantly with increasing concentrations of halothane. These findings suggest that among the inspiratory muscles in kittens the genioglossus, which maintains upper airway patency during inspiration, is most vulnerable to halothane anesthesia at or below the concentration of 1 MAC. As the MAC for halothane determined in kittens (1.39% ± 0.03%) was significantly larger than that in cats, it is probable that, at equipotent anesthetic concentrations, kittens experience greater upper airway obstruction and respiratory depression than do adult cats.

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The respiratory system of infants and young children differs in structure and in function from that of adults (1). The thorax is small in relation to the abdomen, and the sternum is soft, providing an unstable base for the rib cage. The diaphragm rides high, and its motion is limited by the large abdomen (1). The rib cage is cartilaginous, and the intercostal muscles are poorly developed. Therefore, the chest wall in infants is too compliant to resist negative pleural pressure, and retracts with inspiration. Consequently, under general anesthesia functional residual capacity tends to decrease, resulting in airway closure (1). It is likely, therefore, that the administration of central nervous system depressants such as inhaled anesthetics and narcotics, and the incomplete reversal of muscle relaxants, would have more profound effects in this young age group than in adults (1,2).

The activity of the upper airway muscles, particularly that of the genioglossus, which maintains upper airway patency during inspiration (3), can easily be depressed by anesthetics such as halothane and enflurane. By contrast, the degree of depression of phrenic nerve-diaphragm activity is less than that of hypoglossal nerve-genioglossus activity (4,5). These findings suggest that the various inspiratory muscles and their motor innervation have differential sensitivity to anesthetics. Indeed, our recent studies (6) demonstrated that halothane anesthesia depressed the electromyographic (EMG) activity of inspiratory muscles in cats in a dose-dependent fashion. This effect was greater in the genioglossus, less in the intercostal muscles, and least in the diaphragm.

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Whether this differential sensitivity among inspiratory muscles in developing animals differs from that in adults, however, has not been investigated. In the present study we measured the EMG response of the diaphragm, the external intercostals, and the genioglossus to increasing concentrations of halothane in spontaneously breathing kittens to see if their inspiratory muscles behave differently from those of mature cats.

Methods

With the approval of the Institutional Animal Care and Use Committee, we studied seven 2-mo-old kittens weighing 0.56 ± 0.058 kg (range, 0.49–0.59 kg). Anesthesia was induced with 1.5%–2.5% halothane in oxygen via a face mask. The animals breathed spontaneously throughout the experiments. A high flow (6 L/min) of halothane-oxygen mixture was blown into the face mask under a slight positive pressure (<2 cm H_2O), both to provide anesthesia and to prevent dilution of the gas mixture by room air and rebreathing of CO_2. The face mask was connected to a nonrebreathing circuit, comprising one-way valves and a fully expanded 0.5-L reservoir bag. In a pilot study, a catheter tip was inserted in a naris for continuous monitoring of the CO_2 concentration in inspired and expired gas; the concentration of CO_2 in inspired gas was too low to be detected by the CO_2 analyzer, indicating that the circuit was nonrebreathing. This catheter was not used in the experiments because a foreign body in the airway could alter the genioglossus activity. The halothane vaporizer (Draegerwerk, Luebeck, Germany) was calibrated with a mass spectrometer (Perkin-Elmer MGA100, Pamona, Calif.) against standard test gas mixtures. After the induction of anesthesia, a catheter was inserted into the left femoral artery for arterial blood gas sampling and blood pressure monitoring. Body temperature was monitored by a rectal thermistor and was kept within normal limits for cats (37.0–39.0°C) using a warming light and blanket.

The EMG electrodes were multistrand stainless steel wires with Teflon insulation (Bergen Cable Technical Co., Lodi, N.J.). The wire was threaded through a 21-gauge needle, and about 0.5 mm of the insulation was scraped off at the tip. The bare tip was then bent toward the needle barrel. A pair of EMG electrodes was inserted into the genioglossus, the intercostal muscle, and the diaphragm using a guided-needle technique (7). In addition, a reference electrode was inserted into the hind leg muscles. Electrodes in the diaphragm were inserted transcutaneously into the crural portion using a technique described previously (8). A second pair was inserted into the costal diaphragm under direct exposure through a skin incision on the anterolateral costal margin. Electrodes in the intercostal muscle were inserted into the right fifth or sixth posterior intercostal space, approximately 1 mm apart, under direct vision through a skin incision just below the scapula. The incisions were subsequently closed. To expose the genioglossus muscle, which was small and difficult to identify, an anterior submental midline incision was made through the skin and fascia, and electrodes were inserted under direct vision. Surgical preparation was carried out under 1.5%–2.0% halothane-oxygen anesthesia. After all electrodes were inserted, the animals were turned prone and breathed spontaneously without an artificial airway or tracheal tube. Because a change in head position alters genioglossus activity (9), care was taken to keep the head stable throughout the study. At the end of the experiment, the animals were killed by injection of excessive pentobarbital. The positions of all electrodes were confirmed at necropsy.

The raw EMG signals were amplified by a DC preamplifier (model EMA 830, CWE, Ardmore, Pa.) and high-impedance head-stage amplifiers (model HSA-830, CWE, Inc.). Signals were amplified 1000–10,000 times (noise and artifacts were filtered below 50 Hz and above 5 kHz) and recorded on an electrostatic recorder with a linear frequency response up to approximately 5 kHz (model ES 1000, Gould, Cleveland, Ohio). Electromyographic signals were also rectified and integrated (moving time average, MTA) by an RC circuit (SA-414 Analog Processor, Service Associate, San Diego, Calif.), with a time constant of 50 or 100 ms. We chose the appropriate value for the animal according to the respiratory frequency, and kept it constant throughout any given study. The MTA and the raw EMG signals were recorded on a multichannel recorder (10) (Figure 1). Inspiratory activity was defined as the difference between the end-expiratory baseline MTA and the peak during inspiration (peak height of MTA).

Preliminary studies revealed that an inspiratory halothane concentration of 2.5% or more resulted in either extreme hypoventilation or apnea, and most animals awoke at concentrations less than 1.0%. The experiments were, therefore, performed at halothane concentrations of 1.0%, 1.5%, and 2.0%. We used the data obtained at 1% halothane as control values, as measurements at zero inspired halothane could not be obtained without the use of sedatives, which depress the inspiratory muscle activity.

The concentration of halothane in the face mask, as measured with a mass spectrometer, reached the inflow concentration within 30 s after the vaporizer concentration was adjusted. Pilot studies in kittens with a tracheal tube showed little difference between inspired and end-expiratory halothane concentrations within 5 min after a change in the vaporizer

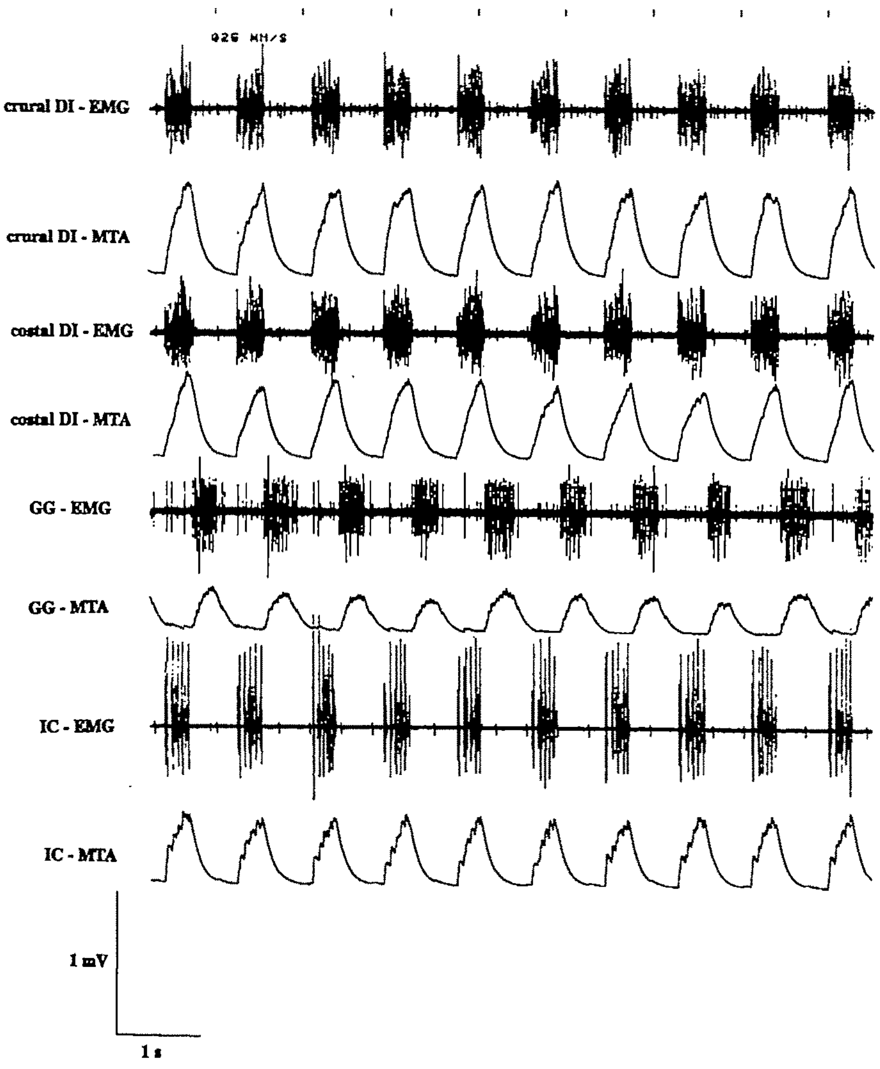

Figure 1. A typical recording of an electromyogram (EMG) and its moving time average (MTA) of three inspiratory muscles at 1.0% halothane in a kitten (control). DI, diaphragm; GG, genioglossus; IC, external intercostal muscle.

setting. Moreover, 5 min after a change in the inspired halothane concentration, EMG activity of each muscle was stable and reproducible. We concluded that 20 min was more than sufficient time for equilibration to a steady state after a change in halothane concentration.

After surgical preparation, the concentration of halothane in oxygen was increased to 2.0% for 20 min, and arterial blood gas tensions were measured. The Pa_{CO_2} value obtained at 2.0% halothane was maintained throughout the study by adding CO_2 to the inspired gas mixture to keep the chemical stimuli to the respiratory centers constant. The electromyogram and its MTA were recorded at paper speeds of 10, 25, and 100 mm/s. Halothane concentration was decreased by 0.5% and maintained for at least 20 min before an arterial blood sample was taken for analysis, and an EMG recording was made at the new concentration.

We measured the peak height of the MTA (in inches), respiratory frequency (f), inspiratory time (T_I), inspiratory duty cycle, or the ratio of T_I and total respiratory cycle duration (T_I/T_{TOT}), using a digitizer and a computer system. At least 30 consecutive breaths were analyzed from recordings on the polygraph paper at each concentration in each animal, and mean values were obtained. As peak height is a dimensionless number, it was expressed as percent of the control value at 1.0% halothane.

In separate studies, the minimum alveolar concentration (MAC) of halothane in oxygen was measured in 1- and 2-mo-old kittens. The animals were anesthetized via a face mask by halothane in oxygen, and the trachea was intubated. End-tidal concentrations of halothane, CO_2, and oxygen were measured by a mass spectrometer. Supramaximal stimulation was given by tail clamping. End-tidal halothane concentration initially was 0.8%–0.9%; it was increased by 0.1%–0.2% steps to the concentration at which the response to stimulation was abolished. Minimum

Table 1. Effect of Halothane Anesthesia on Inspiratory Muscle Activity[a] in 2-Month-Old Kittens ($n = 7$)

Concentration (%)	Diaphragm			
	Costal	Crural	Intercostals	Genioglossus
1.0	100	100	100	100
1.5	61.8 ± 7.3^{b}	71.8 ± 5.8^{b}	68.9 ± 9.6^{c}	$0.0 \pm 0.0^{b,d}$
2.0	54.5 ± 6.2^{b}	66.6 ± 4.5^{b}	$35.4 \pm 8.8^{b,d,e}$	$0.0 \pm 0.0^{b,d}$

[a] Expressed as percent of peak height of moving time average from that at 1% halothane (control).
[b] $P < 0.01$ compared with control.
[c] $P < 0.02$ compared with control.
[d] $P < 0.01$ compared with diaphragm (crural).
[e] $P < 0.01$ compared with value at 1.5%.

alveolar concentration was calculated, and mean values were obtained as previously described (11).

Repeated measures analysis of variance with Bonferroni's multiple comparison was used to compare the MTA of a single inspiratory muscle at different concentrations (intraindividual comparison). The absolute values of MTA in inches were analyzed. Repeated measures analysis of variance was also used to compare the percent depression of MTA of different inspiratory muscles at a given concentration of halothane (interindividual comparison). Student's *t*-test was used to compare the MAC values in the two age groups. A probability value of less than 5% was considered statistically significant.

Results

The MAC of halothane in oxygen was 1.30% ± 0.01% (mean ± SEM) in 1-mo-old kittens ($n = 3$) and 1.39% ± 0.02% in 2-mo-old kittens ($n = 3$). The end-tidal concentration of CO_2 was less than 8.0% during determination of MAC. The MAC value in 2-mo-old kittens was significantly more than that measured by us in adult cats (1.21% ± 0.04%) (6).

During spontaneous breathing, Pa_{CO_2} in kittens increased to 59.0 ± 3.3 mm Hg at 2.0% halothane in oxygen, and was more than 80 mm Hg at 2.5%. Therefore, Pa_{CO_2} was kept near 60 mm Hg (59.3 ± 1.8 mm Hg; range, 56–62 mm Hg) throughout the experiments while the concentration of halothane varied from 1.0% to 2.0%. Mean arterial pH was 7.22 ± 0.08 in a range of 7.18–7.27. Mean Pa_{O_2} was 387 ± 37 mm Hg, and all measurements were more than 300 mm Hg. Systolic blood pressure was lowest (mean value of 108 mm Hg) during 2.0% halothane and was highest (mean value of 123 mm Hg) during 1.0% halothane.

The peak height of the MTA of the electromyogram for the diaphragm and intercostals decreased with increasing halothane concentration (Table 1). The genioglossus lost its phasic inspiratory activity at both 1.5% and 2.0% halothane in all kittens. Crural and costal diaphragmatic activity and intercostal activity at 1.5% and 2.0% halothane were significantly less than values at 1% halothane. Crural diaphragmatic activity decreased the least, and at 2.0%, intercostal activity was attenuated significantly ($P < 0.01$) more than was crural diaphragmatic activity. Figures 1 and 2 show typical raw EMG tracings from the diaphragm, the intercostals, and the genioglossus and their MTA under 1% halothane (control) and 2% halothane from the same 2-mo-old kitten.

Respiratory frequency, T_I, and T_I/T_{TOT} did not change significantly with increasing concentrations of halothane, with the exception of frequency at 1.5%, which was slightly and significantly ($P < 0.05$) increased (Table 2).

Discussion

The genioglossus muscle contracts synchronously with the diaphragm and plays an important role in the maintenance of upper airway patency during the respiratory cycle. The relaxation of the genioglossus displaces the tongue posteriorly and results in upper airway obstruction (1). Recent studies in animals and in humans have shown that the activity of the hypoglossal nerve and the genioglossus is attenuated by barbiturates (4,5), sleep (12–14), ethanol (15), and anesthetics (16).

Hwang et al. (16) demonstrated selective depression of phasic hypoglossal motor activity over phrenic nerve activity in decerebrate cats that were paralyzed, tracheally intubated, and mechanically ventilated. Nishino et al. (4,5) also reported similar findings in vagotomized cats that were paralyzed and ventilated through the tracheostomy.

The activity of the genioglossus muscle is influenced importantly by the negative pressure in the upper airways during inspiration (17,18) and by the position of the head and neck (9). In animal experiments in which a tracheostomy or endotracheal tube is used, the activity of the hypoglossal nerve and genioglossus is modified, and the pressure on the

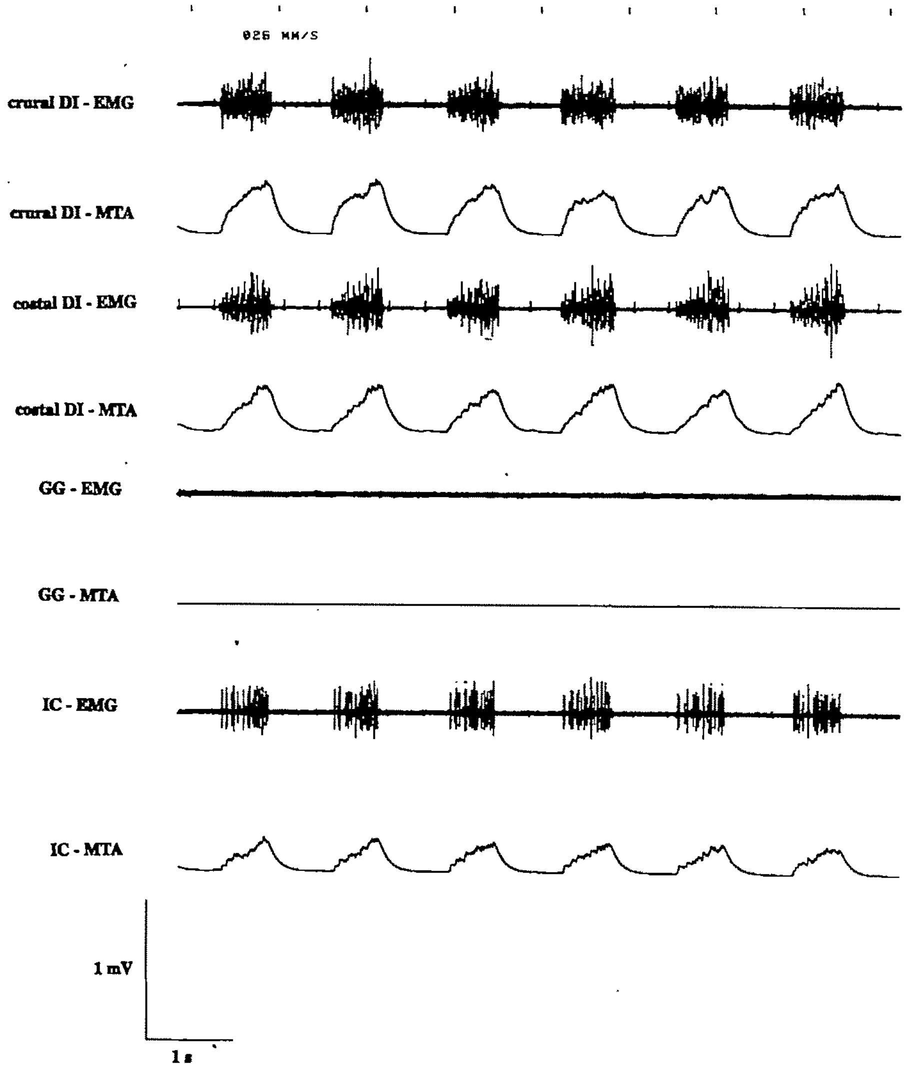

Figure 2. A typical recording of an electromyogram (EMG) and its moving time average (MTA) of the same muscles at 2.0% halothane in the same kitten. DI, diaphragm; GG, genioglossus; IC, external intercostal muscle. Note that the phasic electromyographic activity of the genioglossus is abolished.

Table 2. Effect of Halothane Anesthesia on Respiratory Frequency and Timing Component in 2-Month-Old Kittens ($n = 7$)

Concentration (%)	f (min^{-1})	T_I (s)	T_I/T_{TOT}
1.0	61.7 ± 4.2	0.43 ± 0.03	0.43 ± 0.02
1.5	66.6 ± 4.4[a]	0.43 ± 0.03	0.45 ± 0.01
2.0	62.3 ± 4.0	0.46 ± 0.03	0.47 ± 0.01

T_I, inspiratory time; T_{TOT}, total respiratory cycle duration; T_I/T_{TOT}, respiratory duty cycle.

[a] $P < 0.05$ compared with value at 1.0%.

upper airway mucosa remains atmospheric. Furthermore, the tracheal tube itself probably affects genioglossal activity by mechanical stimulation and displacement of the tongue. Vagotomy and carotid denervation also modify genioglossal activity (19). Thus, previous studies did not necessarily represent the physiologic response of inspiratory muscles to anesthetics.

In the present study, the kittens were breathing spontaneously, and genioglossal activity was not modified artificially by either injury or instrumentation. Physiologic temperature, intravascular fluid balance, and oxygenation were also maintained throughout the experiments. Our results, therefore, most likely represent physiologic responses of inspiratory muscles to increasing concentration of inhaled anesthetics. As anesthetic concentration was varied, Pa_{CO_2} was maintained at approximately 60 mm Hg, the value that was measured when the inspired halothane concentration was 2%. Although this level of Pa_{CO_2} may not be physiologic, it was necessary to maintain an isocapnic level throughout the experiments to keep the chemical stimuli to the bulbopontine respiratory centers constant, as well as to maintain phasic inspiratory activity of the genioglossus. Inspiratory phasic activity has been found to be inconsistent or absent during normocapnia in kittens (20).

We demonstrated a differential sensitivity of three inspiratory muscles to halothane anesthesia in kittens. All three muscles showed a dose-related response to increasing concentrations of halothane. The genioglossus was most sensitive to halothane, the intercostals were less so, and the crural diaphragm was least sensitive to the depressant effect of halothane.

The sensitivity to halothane of the genioglossus, which completely lost its phasic activity at 1.5% and 2.0%, was far greater than that observed recently in adult cats in our laboratory under essentially identical experimental conditions. In the cats, phasic genioglossal activity was decreased but present at concentrations of halothane as high as 3.0% (6). The depression of the intercostals and the diaphragm in the kittens was not significantly more than that in the adult cats we studied. Because the MAC for halothane determined in our laboratory was significantly higher in kittens than in cats, however, more notable, or even significant, differences in intercostal activity might have been observed under equipotent anesthetic conditions.

Our pilot studies in 3-wk-old kittens showed irregular and inconsistent genioglossal activity even at 1.0% halothane (unpublished data). Electromyographic studies by Watchko et al. (21) of 1-mo- and 2-mo-old kittens in response to acute hypoxia and hypercapnia also indicate immaturity of the genioglossus relative to the diaphragm. These findings suggest that maturation of the hypoglossal-genioglossus system is slower than that of the phrenic-diaphragm system or the spinal-intercostal system. Brozanski et al. (22) studied morphologic maturation of genioglossal motoneurons in developing kittens and demonstrated a linear increase in the motoneuron surface area from 3 days to 2 mo of age. Their findings suggest that the greater depression of genioglossal activity in the kittens is due to immaturity of motoneurons and their dendritic connections.

Studies of respiratory control in response to acute hypoxia by Watchko et al. (21) and Bonora et al. (23) suggest that, in terms of the development of its respiratory control mechanism, a 2-mo-old kitten is equivalent to a human newborn infant of 2–4 wk of age. Beyond 4 wk the biphasic ventilatory response to acute hypoxia changes to a more mature, sustained ventilatory response (24). From our findings in 2-mo-old kittens and in adult cats, assuming similarity between cats and humans in their respiratory control and response to anesthetics, one might speculate that infants and young children are more vulnerable to the depression of genioglossal activity and resultant upper airway obstruction during inhalation anesthesia than are older children and adults.

In addition, because the thoracic wall in infants and young children is highly compliant, requiring tonic and phasic intercostal muscle activities to sustain its rigidity and withstand negative pleural pressure (1), depression of intercostal muscle tension and activity by anesthetics can result in paradoxic breathing, increased energy cost of breathing, inspiratory muscle fatigue, and more pronounced reductions in resting lung volume and tidal breathing. These effects may contribute to respiratory depression, ventilation/perfusion imbalance during and after anesthesia, and the high incidence of early postanesthetic hypoxemia seen in the pediatric age group (2).

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Use of Patient-Controlled Analgesia to Compare the Efficacy of Epidural to Intravenous Fentanyl Administration

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Fentanyl, unlike morphine, is highly lipophilic and rapidly diffuses out of the epidural space. Respiratory depression is, therefore, unlikely when fentanyl is given epidurally. However, much of fentanyl's analgesic effect is mediated by systemic rather than spinal receptor binding. To test this hypothesis, we performed a prospective, double-blind, cross-over study comparing epidural and intravenous (IV) administration of fentanyl in 16 patients for the first 12 h after lower abdominal or lower extremity surgery. To allow direct comparison of these two routes of administration, patient-controlled analgesia was used so patients could self-titrate their analgesia. Patients were randomized to receive fentanyl initially by an epidural (group A, $n = 8$) or IV (group B, $n = 8$) catheter for 6 h, after which they were crossed-over to the alternate route by means of a hidden three-way stopcock. The degree of analgesia was subjectively evaluated by a visual analogue scale, and by an observer rating patient's comfort and sedation. Cumulative dosage of fentanyl was recorded, and plasma fentanyl concentrations were measured. The onset of analgesia and increase in plasma fentanyl concentrations were more rapid with intravenous fentanyl. However, after 60 min, analgesia (visual analogue scale 2–4 cm) or plasma fentanyl concentrations (0.3–0.7 ng/mL) did not differ between the two routes of administration. There were also no significant differences in the cumulative dosage of fentanyl within each group (epidural vs IV) or between the groups. Thus, the analgesic effects of epidural fentanyl appear largely mediated by systemic absorption. Intravenous fentanyl achieves a similar degree of analgesia and a more rapid onset of effect without the need for epidural catheterization.

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Opiate analgesics are commonly used to alleviate acute postoperative pain. Isolation of spinal opiate receptors (1) and subsequent demonstration of the efficacy of epidural opiate administration resulted in increasing popularity of this route of opiate administration for pain management (2). The initial studies of epidural opiate administration demonstrated that relatively small doses of morphine provided dramatic analgesia of long duration (3), persisting long after morphine plasma concentrations decreased below accepted analgesic levels. Although morphine has a direct spinal action, its slow onset of action is secondary to its poor lipophilicity. This results in the slow transfer of morphine across the dura into the cerebrospinal fluid, where a large depot is created that provides for a prolonged spinal analgesic effect (4). However, this depot results in rostral spread of morphine to the brainstem with possible pruritus, nausea, vomiting, and late respiratory depression (5).

In contrast, a more lipophilic agent will have a more rapid onset of action and will also be absorbed rapidly from the cerebrospinal fluid with less risk of rostral spread. Fentanyl and sufentanil are potent opiates that are highly lipophilic (blood: oil partition coefficient 813 and 1778, respectively) and rapidly cross the dura. However, they may also rapidly diffuse into epidural vessels and have a primarily systemic effect. Therefore, it is important to establish if epidural administration of the more lipophilic opiates really provides an advantage over direct systemic administration.

Patient-controlled analgesia (PCA) enables patients to self-titrate bolus doses of analgesic agents to their desired level of pain relief by using a programmable infusion pump. This individualizes the dose required to maintain adequate analgesia according to the patient's needs and provides a means of comparing the subjective analgesic effects of different drugs

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and/or routes of administration in a heterogeneous population.

This prospective, double-blind, randomized crossover study was designed to establish whether there is a difference in the dose requirements for fentanyl or in its plasma concentration when it is administered epidurally or intravenously by means of a PCA device.

Methods

The study was approved by the Human Investigation Review Board of the Durham Veterans' Affairs Medical Center. Each patient signed a written informed consent form. ASA physical status I–III patients admitted for lower extremity or abdominal surgical procedures that would require a potent analgesic for postoperative pain management were included. The night before surgery, patients were instructed how to use a PCA device (Abbott Life Care-Abbott Laboratories, Chicago, Ill.) and to describe pain on a visual analogue scale (VAS)—a 10-cm straight line marked with "no pain" at 0 cm and "worst imaginable pain" at 10 cm. Patients were encouraged to use the PCA to maintain a satisfactory level of pain relief.

Patients were premedicated with diazepam, 10 mg orally, 1–1.5 h before surgery. Two intravenous (IV) catheters were placed, one in the antecubital fossa of the arm opposite that through which fentanyl would be administered. Before induction of anesthesia, a lumbar epidural catheter was placed at the L3-4 or L4-5 interspace. Correct position of the catheter within the epidural space was confirmed by the establishment of neural blockade after the injection of 10 mL of 1.5% lidocaine. General anesthesia was then induced with an IV induction agent and maintained with a potent volatile anesthetic. No opiate was given during the preoperative or intraoperative period. When the patients were awake enough to follow instructions after the completion of surgery, the use of the PCA device and VAS was explained again. Each PCA device was loaded with fentanyl diluted to 10 μg/mL. Patients were then randomly assigned to receive fentanyl via the PCA for the next 6 h either epidurally (group A) or intravenously (group B). The PCA device was connected to both the IV catheter and the epidural catheter by means of a hidden three-way stopcock. At the end of 6 h, the stopcock was rotated by a person not involved in the evaluation of the patient, and the treatments were crossed-over. Thus, fentanyl administration was switched from the epidural to the IV route in group A patients and from the IV to the epidural route in group B patients for the second 6 h. The patients and the evaluating nurse were blinded to the route of fentanyl administration.

When patients first complained of pain, an initial dose of fentanyl, 1 μg/kg, was administered via the PCA device either epidurally or intravenously according to the randomization schedule. All subsequent doses of fentanyl were self-administered by the patient. The maintenance dose was set at 20 μg (i.e., 2 mL) fentanyl with a lockout interval of 6 min. The cumulative fentanyl dose was recorded during the 12 h of the study. Pain relief was scored subjectively by the patient by means of the VAS before fentanyl administration and then at 1, 3, 5, 15, 30, 60, 120, 240, 360, 420, 480, 600, and 720 min. At the same time intervals, the recovery room nurse independently estimated the patient's level of observed comfort and assigned it a score as follows: 0 = none, 1 = fair, 2 = good, 3 = excellent. The level of sedation was simultaneously assessed on a four-point scale: 0 = none, 1 = drowsy, 2 = somnolent but easily arousable, 3 = asleep or somnolent and difficult to arouse. Blood samples for plasma fentanyl content were obtained from the antecubital venous catheter at 1, 3, 5, 15, 30, 60, 120, 240, 360, 420, 480, 600, and 720 min after the initial dose was given. These samples were drawn into heparinized containers and placed in ice. Plasma was separated by cold centrifugation and stored at −70°C. Fentanyl concentrations were measured using a radioimmunoassay technique. The sensitivity of the assay was 0.1 ng/mL, and the coefficient of variation ranged between 5% and 9% at concentrations of 0.1 and 8.0 ng/mL, respectively. Patients were maintained in the postanesthesia care unit for the entire study duration.

Multivariate tests of VAS, comfort and sedation score, cumulative fentanyl dose, and fentanyl plasma concentration were performed to assess the effectiveness and dosing of analgesia between the routes of administration. Probabilities were obtained associated with the effects of group (A or B), hour of study, and cross-over (first 6 h and second 6 h). Because data were collected hourly, a repeated measures analysis of variance, multivariate in the sequential data and with the order of the two routes of drug administration included as an independent effect, was used. Order of cross-over itself was a repeated element for each patient, so the univariate model was also set up as a repeated measures design with appropriate blocking of patients as one of the independent elements. Pearson correlation coefficients were derived to describe the relationship between VAS and plasma fentanyl concentration. A P value of less than 0.05 was considered significant.

Results

Demographic data from all 16 patients are presented in Table 1. In group A, six patients had lower limb

Table 1. Demographic Data of Patients Studied

	Group A	Group B
Age (yr)	57.6 ± 4.6	60.6 ± 2.0
Weight (kg)	70.8 ± 1.7	74.3 ± 3.8
Height (cm)	171.2 ± 2.4	168.7 ± 2.2

Values are mean ± SEM.

orthopedic procedures and two patients lower abdominal surgery. In group B, four patients had lower extremity orthopedic procedures and four patients lower abdominal procedures.

The onset of analgesia was more rapid with IV than epidural fentanyl. This is illustrated by a significantly lower VAS score in group B patients at 15 min (Figure 1). Thereafter there was no significant difference in analgesia between the two routes of administration. After 2 h, patients in both groups tended to titrate their analgesia to a VAS of 2–4 cm (mild pain). Sedation and comfort scores were similar between both groups (Figures 2 and 3).

There were no statistically significant differences between groups A and B with respect to the cumulative hourly dose of fentanyl, the 12-h cumulative dose of fentanyl, or the cumulative doses of fentanyl during epidural or IV administration (Table 2). Within groups A and B there were no significant difference between fentanyl usage in the first 6 h and second 6 h (Table 2), i.e., before and after cross-over.

There were no significant differences in plasma fentanyl concentration whether it was administered epidurally or intravenously. Although fentanyl plasma concentrations were numerically higher in the first 30 min in group B (IV first) than group A (epidural first), they were not significantly different. Thereafter, plasma concentrations stabilized at 0.5 ng/mL in both groups (Figure 4). There were no significant differences in plasma fentanyl concentrations at equivalent time periods between the first and second 6 h.

There was a high inverse correlation between VAS and plasma fentanyl concentration (i.e., VAS decreased as plasma fentanyl increased) during epidural administration ($r = -0.63$, $P = < 0.01$), but the correlation during IV administration was negligible ($r = -0.03$, $P = 0.91$).

Discussion

It is almost impossible to objectively measure the quality of analgesia, making it very difficult to establish the true relative efficacy of different analgesic drugs or routes of administration. The PCA pump enables patients to self-titrate analgesia to their desired pain relief and then to maintain it at that level. In other words, PCA provides a closed-loop system that maintains a fairly constant level of analgesia for an individual patient (6). This enables effective equianalgesic comparisons to be made between different drugs and different routes of drug administration (7,8) and negates the effect of pharmacokinetic, pharmacodynamic, and psychologic variability (9).

There was no difference in this study in the analgesic efficacy of epidural versus IV administration of fentanyl when patients were allowed to self-titrate their analgesic requirements using a PCA device. This was evaluated by a subjective criterion (VAS), patient observation (comfort score, sedation score), and pharmacologic data (cumulative fentanyl dose, fentanyl plasma concentration). Although the size of the groups was relatively small, retrospective power analysis estimated that this sample size, with the degree of variability obtained, would have a power of 87% in detecting a within-group difference of 125 μg in the 6-h cumulative dose of fentanyl and an 82% power of detecting a within-group 0.125-ng/mL difference in the average fentanyl plasma concentration.

The patients showed no difference in baseline and subsequent VAS pain scores. This indicates that both groups started off with similar amounts of pain and that fentanyl PCA via either the epidural or IV route allowed the patients to achieve and maintain equivalent levels of analgesia. Patients in both groups were able to titrate their analgesia to a VAS of 2–4 cm (i.e., mild pain) after the first 2 h and then maintain it at this level for the remainder of the study. This degree of analgesia is consistent with the levels of analgesia that are routinely achieved with PCA (7,8).

After the first hour, the analgesic efficacy of fentanyl by PCA was similar with epidural or IV administration, as were the cumulative fentanyl doses and measured plasma fentanyl concentrations. Welchew (10) reported that a single dose of 100 μg (2 mL) of epidural fentanyl resulted in significant systemic concentrations of fentanyl that were within its accepted analgesic range. This is in contrast to the study by Gourlay et al. (11) in which they were unable to measure fentanyl concentrations above 0.1 ng/mL after a single epidural dose of fentanyl, 1 μg/kg. Sufentanil (another highly lipid soluble opiate) given as a single dose (150 μg) either epidurally or intravenously resulted in systemic concentrations, after 15 min, that were similar irrespective of the route of administration (12). In another study, 30 μg of epidural sufentanil also provided similar plasma concentrations to those resulting from the same dose given intravenously. The epidural dose also did not provide any opioid-sparing for postoperative analgesia (13).

Several studies have also compared the continuous infusion of fentanyl given either epidurally or intra-

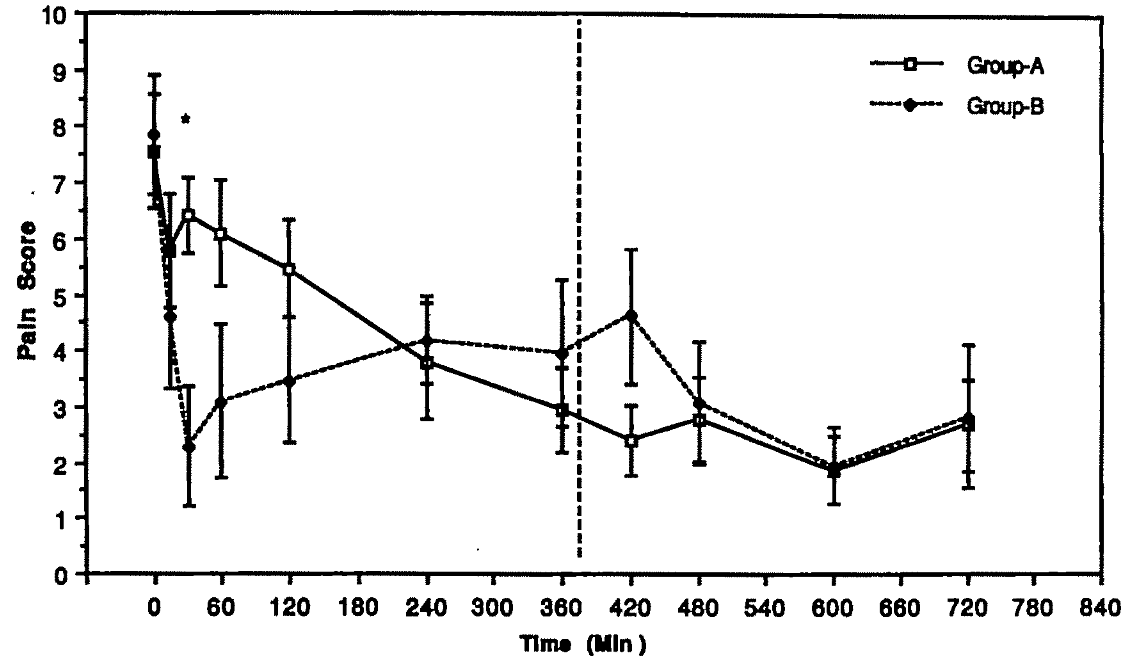

Figure 1. Mean (± SEM) pain scores (as measured by VAS) after patient-controlled administration (PCA) of fentanyl either epidurally or intravenously. Pain scores after the IV administration of fentanyl were statistically lower during the first hour than in the epidural group ($P < 0.05$).

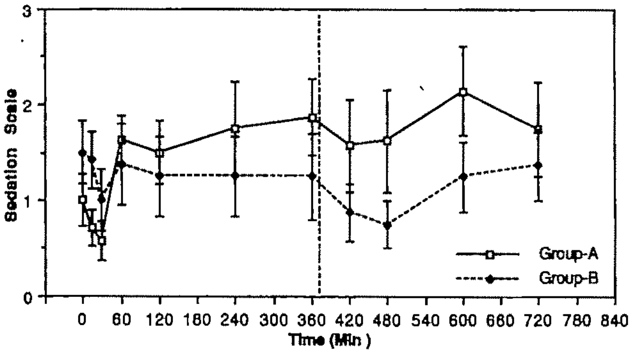

Figure 2. Mean (± SEM) sedation scores after patient-controlled administration (PCA) of fentanyl either epidurally or intravenously. No difference was found between the two routes of administration on the level of sedation as measured on the four-point scale: (0 = no sedation, 1 = drowsy, 2 = somnolent but easily arousable, 3 = asleep or somnolent and difficult to arouse).

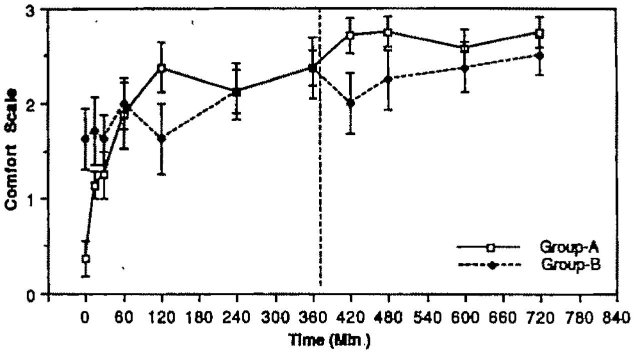

Figure 3. Mean (± SEM) comfort scores after patient-controlled administration (PCA) of fentanyl either epidurally or intravenously. No difference was found between the two methods of administration in the level of comfort (0 = none, 1 = fair, 2 = good, 3 = excellent).

venously (14–16). Loper et al. (14) found equivalent analgesia after knee surgery with either continuous epidural or IV infusion of fentanyl, with similar mean plasma fentanyl concentrations (1.8 ± 0.4 and 1.7 ± 0.4 ng/mL, respectively). In postthoracotomy patients, a continuous infusion of fentanyl at 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ via either a lumbar epidural or IV catheter resulted in equivalent plasma concentrations of fentanyl (1–2 ng/mL) (15). After cesarean section, the infusion rate of fentanyl required to produce adequate analgesia was similar whether given intravenously or epidurally (16). All three of these studies demonstrated sustained plasma concentrations of fentanyl that exceeded 1 ng/mL after both epidural and IV administration. Additional analgesia was given for breakthrough pain in these studies but no adjustments were made to minimize the infusion rate of fentanyl. As the dose was not titrated, a relative overdose of fentanyl may have been administered via the epidural route, resulting in higher systemic concentrations than were found in our study. However, these studies support the premise that an important component of the analgesia after the epidural administration of fentanyl may be provided by its systemic absorption.

Table 2. Dose of Fentanyl During Self-Administration via Either the Intravenous or Epidural Route

Time (h)	Group A	Group B	Combined
1	**157.0 ± 32**	104.6 ± 32.6	130.8 ± 41.4
2	**213.3 ± 44.3**	152.1 ± 69.4	182.7 ± 64.5
4	**309.4 ± 69.5**	209.6 ± 78.6	259.5 ± 88.3
6	**389.6 ± 95.8**	285.9 ± 148.6	337.8 ± 132.1
7	419.6 ± 89.5	**324.6 ± 169.6**	372.1 ± 139.9
8	462.1 ± 97.5	**366.4 ± 212.5**	414.3 ± 167.2
10	538.9 ± 122	**472.5 ± 343.1**	508.2 ± 250.8
12	619.6 ± 151.6	**530.0 ± 393**	574.8 ± 291.6
Mean hourly cumulative dose	56.6 ± 45.1	47.7 ± 47.2	52.1 ± 46.2
Total epidural use	**389.6 ± 95.8**	**244.1 ± 257.7**	**316.9 ± 194.4**
Total intravenous use	230.0 ± 68.7	285.9 ± 148.6	258.0 ± 115.8

Cumulative fentanyl use in micrograms (± SD). The figures in bold depict the period that the patients self-administered fentanyl via the epidural route.

Using the epidural route, the concentration and volume (10) of the fentanyl dose as well as the site of the epidural catheter in relation to the site of surgery is important in providing optimal analgesia with the smallest dose. We used a concentration of 10 μg/mL with a volume of 2 mL as a maintenance dose. This concentration has previously been shown to be optimal for fentanyl via the epidural route (10). To ensure the epidural catheter site was appropriate, it was inserted at the L3-4 or L4-5 interspace and all operations were restricted to those involving the lower extremity or lower abdomen. The use of PCA for fentanyl administration in the present study ensured that the minimal effective dose was given, so that any discrepancy in analgesic requirements between the different routes would have been evident. Under these conditions, there were no differences in fentanyl plasma concentrations between epidural and IV administration when patients self-titrated their fentanyl requirements, and analgesia was achieved at much lower plasma fentanyl concentrations than in studies in which a continuous infusion was used (14–16). Similarly, in another study, the plasma hydromorphone levels after epidural PCA were lower than those achieved by a fixed-rate continuous hydromorphone infusion that obtained the same degree of analgesia (17). Gourlay et al. (18) defined the minimal effective analgesic concentration for IV fentanyl in patients having either upper or lower abdominal surgery as 0.63 ± 0.25 ng/mL, with an average hourly consumption of 55.8 ± 22 μg/h (18). In the present study, whether fentanyl was given epidurally or intravenously, the hourly fentanyl consumption and resultant fentanyl plasma concentrations were similar to those reported by Gourlay et al.

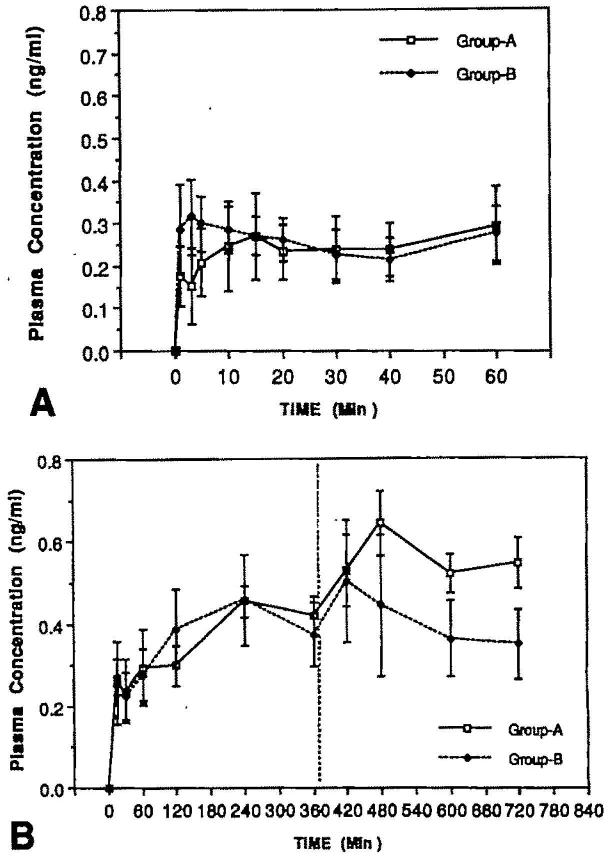

Figure 4. Mean (± SEM) plasma fentanyl concentrations after patient-controlled administration (PCA) of fentanyl either epidurally or intravenously. The plasma concentrations of fentanyl did not differ statistically between the two groups during the first hour (A) or during the remaining 11 h of the study (B).

Welchew and Breen (19) have also recently compared the use of epidural fentanyl to IV PCA in patients admitted for abdominal surgery. They found that both routes of fentanyl administration resulted in equally satisfactory analgesia. In their study, however, the patients receiving IV PCA fentanyl self-administered twice the cumulative dose over 24 h of the group self-titrating their fentanyl via the epidural route. The patients in the two groups received different amounts of fentanyl with each request. The maintenance doses were 20 μg fentanyl in the IV group and 5 μg fentanyl in the epidural group. The cumulative or total dose for IV PCA is significantly altered by the size of the maintenance dose (20,21). In Welchew and Breen's study (19), the IV maintenance dose was four times greater than the epidural maintenance dose, and this may have accounted for the differences in the cumulative dose that resulted between the two routes of fentanyl administration.

In contrast to fentanyl, the epidural PCA administration of morphine or meperidine is associated with a dramatically decreased dose requirement compared with IV PCA (22). Plasma concentrations of morphine and meperidine are well below minimal effective analgesic concentration. This difference is more prominent with morphine, the less lipophilic opiate, than with meperidine because the rate and degree of systemic absorption after epidural administration of an opiate is related to its lipophilicity (23). The epidural administration of fentanyl, a highly lipophilic opiate, should result in plasma concentrations similar to those of an equal dose given intravenously. Therefore, the similar plasma fentanyl concentrations we obtained after repeated dosing, either epidurally or intravenously, are explained by the high lipophilicity of fentanyl. In addition, the ED_{50} of intrathecal fentanyl in rats exceeds the concentration required for epidural use (24). The authors attribute the analgesia obtained from the epidural administration of fentanyl primarily to its systemic absorption and not to its effect on the pain receptors in the dorsal horn of the spinal cord. In view of the significant systemic absorption of fentanyl from the epidural space and the equal dosage requirements between epidural and systemic administration for equivalent analgesia, the value of epidural fentanyl as a sole analgesic agent is uncertain.

The onset of analgesia was slower in the patients initially receiving epidural fentanyl. There are two possible explanations for this. The peak effect of IV fentanyl occurs 2–5 min after IV bolus administration (25), whereas the onset of effect after epidural administration is delayed for 10–20 min (26). This delay may be explained by the time taken for fentanyl to traverse the dura and cerebrospinal fluid and bind to opiate receptors in the neuraxis of the spinal cord. An alternative explanation may be that the analgesic effect of epidural fentanyl is mediated systemically rather than in the neuraxis, and the delay is caused by the time for systemic absorption; in our study, adequate analgesia was obtained by epidural administration once there was an adequate plasma concentration of fentanyl.

We found a significant correlation between plasma fentanyl concentration and VAS pain score during epidural but not during IV fentanyl PCA administration. Blood samples were taken at fixed time intervals and independent of the time of fentanyl administration. Fentanyl displays hysteresis of its concentration–effect relationship (25), with the difference being greatest just after a bolus dose is administered. The poor correlation between fentanyl plasma concentration and VAS scores, when fentanyl was administered by intermittent IV doses via the PCA pump, may be explained by a continuously changing relationship between plasma concentration and effect. However, the administration of fentanyl by bolus dose into the epidural space results in a slower increase and decline in the systemic concentration (i.e., more closely resembling the plasma profile of an IV infusion), thus maintaining a more constant relationship between plasma concentration and effect. The significant correlation between plasma fentanyl concentration and VAS scores with epidural PCA would thus further support the premise that systemic absorption is responsible for a major portion of the efficacy of epidural fentanyl.

In conclusion, a PCA pump was used to establish the efficacy of epidural versus IV administration of fentanyl. The onset of adequate analgesia was slower via the epidural route. However, once equieffective analgesia was obtained, both fentanyl utilization and plasma concentrations were similar between the two routes of administration. Fentanyl's high lipid solubility leads to rapid systemic absorption from the epidural space so that, unlike other less lipid soluble opiates, there is little advantage to its administration by the epidural route. Indeed, IV administration of fentanyl may be preferable because the onset of action is faster and the problems of epidural catheterization are avoided.

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Hemidiaphragmatic Paresis During Interscalene Brachial Plexus Block: Effects on Pulmonary Function and Chest Wall Mechanics

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We studied the effects of unilateral hemidiaphragmatic paresis caused by interscalene brachial plexus block on routine pulmonary function in eight patients. In an additional four patients, we studied changes in chest wall motion during interscalene block anesthesia by chest wall magnetometry. Ipsilateral hemidiaphragmatic paresis, as diagnosed by ultrasonography, developed in all patients within 5 min of interscalene injection of 45 mL of 1.5% mepivacaine with added epinephrine and bicarbonate. Large decreases in all pulmonary function variables were measured in every patient. Forced vital capacity and forced expiratory volume at 1 s decreased 27% ± 4.3% and 26.4% ± 6.8%, respectively ($P = 0.0001$). Peak expiratory and maximum midexpiratory flow rates were also significantly reduced. Interscalene block caused changes in pulmonary function and chest wall mechanical motion that were similar to those published in previous studies on patients with hemidiaphragmatic paresis of pathological or surgical etiology. Interscalene block probably should not be performed in patients who are dependent on intact diaphragmatic function and in those patients unable to tolerate a 25% reduction in pulmonary function.

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Brachial plexus anesthesia by interscalene injection of local anesthetic routinely causes sensory anesthesia of the fourth and fifth, and frequently of the third, cervical nerve. Using radiographic contrast labeling, Winnie (1) demonstrated that this was due to local anesthetic entering the cervical plexus after interscalene brachial plexus injections as small as 10 mL. Local anesthetic entering the cervical plexus at these levels probably results in one-sided diaphragmatic paresis, as the C-3–C-5 nerve roots form the phrenic nerve.

In a prior investigation of 13 healthy patients (2), we found that interscalene block resulted in a 100% incidence of ipsilateral hemidiaphragmatic paresis. Diagnosis was made by ultrasonography (3–5), which clearly demonstrated paradoxical motion of the cephalad border of the zone of apposition of diaphragm to rib cage on the ipsilateral side during forceful sniff (a maneuver that rapidly decreases pleural pressure). Previous studies have shown consistent sizeable reductions in pulmonary function during pathological unilateral phrenic nerve paralysis (6,7) as well as during direct local anesthetic blockade of one phrenic nerve (8).

We determined that alterations in routine pulmonary function tests and chest wall mechanics occur as the result of unilateral hemidiaphragmatic paresis produced by interscalene block and how these pulmonary function test changes might compare to those previously published during complete unilateral pathological phrenic nerve paralysis. Chest wall magnetometry was used to characterize the physiologic alterations in chest wall motion that occurred during the hemidiaphragmatic paresis that resulted from interscalene block.

Methods

After approval from our Institutional Review Board and written informed consent had been obtained, eight consecutive adult patients were studied. Patients were ASA class I–III and had been scheduled for upper extremity orthopedic procedures under interscalene brachial plexus anesthesia. Two patients had preexisting pulmonary disease (patient 3, moderate chronic obstructive pulmonary disease and patient 7, asthma). No premedication or sedation was

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given until all testing was completed. Interscalene block was administered with the needle tip at, or caudad to, cricoid level according to the method of Winnie (1). A single paresthesia technique with a 23-gauge 2.5-cm needle was used. Each patient received 45 mL of 1.5% mepivacaine with 5 μg/mL of epinephrine and 0.05 mEq/mL of sodium bicarbonate.

Before anesthesia, real-time ultrasonography (Diasonics DRF-400, 3-MHz transducer) of the ipsilateral hemidiaphragm was done to confirm normal caudad motion during sniff. After application of noseclips, data were collected during two successive forced vital capacity maneuvers into a computerized bell spirometer (Warren E. Collins, Eagle II, Braintree, Mass.) with coaching by a respiratory therapist. Expiratory and inspiratory flow-volume curves were then generated by forced expiration and inspiration into a Wedge Spirometer (Med Science, St. Louis, Mo.). X-Y flow-volume data were recorded from a dual-trace storage oscilloscope (Tektronix, Beaverton, Ore.) for later analysis. These measurements were repeated 5 min after completion of interscalene local anesthetic injection, by which time all patients had ultrasonographically diagnosed ipsilateral hemidiaphragmatic paresis (paradoxical cephalad hemidiaphragmatic motion during sniff).

To determine whether a reduction in expiratory function occurred during hemidiaphragmatic paresis that was not based on a reduction in total lung capacity, data were analyzed by volume-indexing the flow-volume curves. This was done by superimposing the curves at the residual volume (RV) points and comparing the postanesthesia peak expiratory flow rate (PEFR) with the baseline flow rate at the same lung volume, as shown in Figure 1.

To analyze the changes in chest wall mechanical motion that occur during interscalene block, an additional four patients were studied using chest wall magnetometry (GMG Scientific, Boston, Mass.). Measurements of anteroposterior diameter changes of the rib cage at midsternum, of the left of the abdomen, and separately of the right half of the abdomen at the umbilical level were made during tidal and deep breathing (Figure 2). Data were recorded immediately before and 15 min after interscalene block and 10 min after ultrasonographically diagnosed hemidiaphragmatic paresis. X-Y plots of these data were photographed from the dual-trace storage oscilloscope.

Results

Ultrasonographic examination revealed that in all eight patients normal ipsilateral hemidiaphragmatic caudad motion changed to paradoxical cephalad motion during forceful sniff within 2 min of interscalene anesthetic injection. Thus, ipsilateral hemidiaphragmatic paresis developed in 100% of the patients studied, as had been observed in our previous study. Spirometry results for patients 3 and 7 who had preexisting obstructive lung disease showed changes during anesthesia that were similar in value to those measured in the six healthy patients.

Table 1 displays the results of routine pulmonary function testing. All eight patients had large reduc-

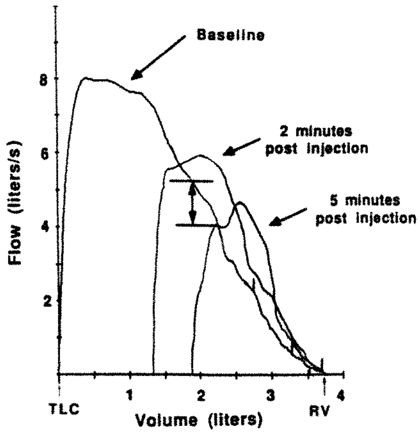

Figure 1. Representative data from a healthy patient comparing baseline (before interscalene block) maximum expiratory flow-volume curve with those measured at 2 and 5 min after interscalene injection of 45 mL of 1.5% mepivacaine with epinephrine. Decreased peak flows at same volumes (referenced to residual volume, RV) constitute evidence that the intact diaphragm normally contributes to forced expiration. TLC represents total lung capacity before interscalene block. See text for discussion.

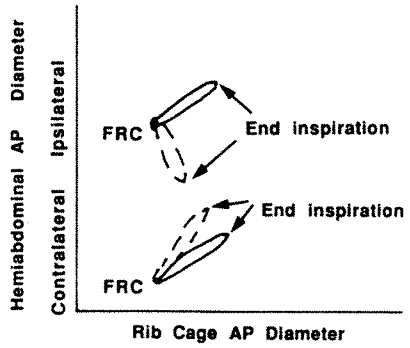

Figure 2. Representative modified Konno-Mead diagram is shown for one of the study patients. Vertical axis, ipsilateral and contralateral hemiabdominal anteroposterior (AP) diameter; horizontal axis, rib cage anteroposterior diameter. Tidal breathing loops beginning at functional residual capacity (FRC) are shown. Ipsilateral hemiabdominal expansion during inspiration changed to contraction (paradoxical motion) during interscalene block in every patient. Contralateral hemiabdominal expansion during inspiration was more preserved. All patients had comparatively more rib cage than abdominal expansion with inspiration during interscalene anesthesia, reflecting recruitment of intercostal and accessory muscles of inspiration to compensate for compromised diaphragmatic inspiratory action. *Solid line,* before anesthesia; *dashed line,* during anesthesia.

Table 1. Comparison of Pulmonary Function Measurements Before and During Interscalene Block

		Spirometry				Flow/volume loop	
Patient No.		FVC (L)	$FEV_{1.0}$ (L)	PEFR (L/s)	FEF_{25-75} (L/s)	PEFR (L/s)	PIFR (L/s)
1	Preblock	3.36	3.02	7.39	3.73	6.0	3.8
	Postblock	2.50	2.20	6.06	2.52	5.1	3.8
	% Change	−25.60	−27.15	−18.00	−32.44	−15.0	0.0
2	Preblock	3.73	3.32	6.50	4.22	5.6	5.9
	Postblock	2.45	2.17	5.25	2.88	5.5	3.3
	% Change	−34.32	−34.64	−19.23	−31.75	−1.8	−44.9
3	Preblock	5.63	4.43	11.80	3.85	8.0	7.5
	Postblock	4.00	3.32	10.40	3.09	7.9	7.3
	% Change	−28.95	−25.06	−11.86	−19.74	−1.3	−2.7
4	Preblock	5.96	4.11	10.00	2.62	7.4	4.0
	Postblock	4.19	3.04	7.60	2.03	6.5	3.9
	% Change	−29.70	−26.03	−24.00	−22.52	−12.2	−2.5
5	Preblock	4.14	3.09	5.18	2.48	5.8	5.0
	Postblock	2.94	2.36	5.12	2.47	4.5	3.8
	% Change	−28.99	−23.62	−1.16	−0.40	−22.4	−24.0
6	Preblock	4.52	3.57	6.99	3.37	8.1	5.5
	Postblock	3.58	2.97	7.72	3.07	8.4	5.8
	% Change	−20.80	−16.81	10.44	−8.90	3.7	5.5
7	Preblock	2.41	1.27	2.37	0.47	1.3	1.0
	Postblock	1.77	0.80	1.36	0.41	1.3	1.8
	% Change	−26.56	−37.01	−42.62	−12.77	0.0	80.0
8	Preblock	4.77	3.98	8.70	4.14	7.0	7.0
	Postblock	3.70	3.17	7.32	3.56	7.0	6.0
	% Change	−22.43	−20.35	−15.86	−14.01	0.0	−14.3

FVC, forced vital capacity; $FEV_{1.0}$, forced expiratory volume at 1 s; PEFR, peak expiratory flow rate; FEF_{25-75}, forced expiratory flow from 25% to 75% of the vital capacity; PIFR, peak inspiratory flow rate.

tions in forced vital capacity (FVC) ranging from 21% to 34% within 5 min of interscalene local anesthetic injection. Mean FVC decreased 27.2% ± 4.3% (P = 0.0001) for the group. Similarly, forced expiratory volume at 1 s ($FEV_{1.0}$) decreased between 17% and 37%, with a mean reduction of 26.4% ± 6.8% (P = 0.0001). Postanesthesia peak expiratory flow rate decreased in all but one patient, with a mean reduction of 15.4% ± 15.7% ($P < 0.05$). Maximum midexpiratory flow rate from 25% to 75% of the vital capacity decreased in every patient with a mean diminution of 17.9% ± 11.1% ($P = 0.05$).

Volume-indexed PEFR decreased 6.0% ± 9.1% ($P = 0.05$) during interscalene block (Figure 1). Inspiratory flow-volume curve analysis showed that peak inspiratory flow rates declined in five of eight patients and was unchanged in one patient. However, these data were less reproducible (Table 1) than expiratory flow and volume data.

Using magnetometry, ipsilateral and contralateral hemiabdominal anteroposterior diameters were plotted as separate functions of increasing rib cage anteroposterior diameter during spontaneous inspiration in four patients. A representative tracing from one of the patients is shown in Figure 2. After interscalene block, rib cage motion was more pronounced than abdominal motion in all four patients. Because of the nature of the measurements, anteroposterior diameter changes by magnetometry may be small during normal or deep breathing as one chest wall compartment may not move at all during breathing. However, the direction of motion and comparison of the chest wall compartments may yield valuable information regarding chest wall muscle function during breathing. In this case, the increase in rib cage activity reflected heightened activity of intercostal and accessory muscles of inspiration (muscles that act on the rib cage and not the abdomen), which are recruited to take over for the compromised diaphragm (9). In addition, paradoxical (inward) ipsilateral hemiabdominal motion during quiet or deep inspiration developed in each patient after receiving interscalene block. By contrast to the ipsilateral side, contralateral hemiabdominal expansion was diminished in three of four patients (and actually increased in the one illustrated patient), but normal directional motion was preserved in all four patients. Thus, the abdomen departed from its usual one degree of freedom of motion (10).

Discussion

In each patient studied, measurements made 5 min after interscalene block injection showed a reduction

Table 2. Percentage Reductions in Pulmonary Function Secondary to Pathological, Surgical, or Interscalene Block-Induced Hemidiaphragmatic Paresis

Year	Investigators	Etiology of hemidiaphragmatic paresis	No. of patients	Decrease in FVC (%)
1967	Fackler et al.	Complete unilateral surgical phrenic nerve section	14	22.7
1967	Gould et al.	Direct local anesthetic infiltration of phrenic nerve	8	29
1975	Arborelius et al.	Pathological paralysis of one hemidiaphragm	17	25
1991	Urmey and McDonald	Interscalene block	8	27

FVC, forced vital capacity.

in pulmonary function similar in magnitude to published results of studies on patients with complete unilateral phrenic nerve paralysis (Table 2) (6–8). For example, the diminution in FVC was 27.2% in our patients. In a study of 14 patients who underwent complete unilateral phrenic nerve section, Fackler et al. (7) found a mean decrease of 22.7% in vital capacity compared to preoperative values. Similarly, in 17 patients with pathological paralysis of one hemidiaphragm, Arborelius et al. (6) found that vital capacity, $FEV_{1.0}$, and maximum voluntary ventilation were each reduced by an average of about 25% of predicted values. In a study of direct infiltration of one phrenic nerve with 25 mL of 1% mepivacaine in eight healthy volunteers, Gould et al. (8) found that inspiratory capacity, vital capacity, and total lung capacity were reduced by 27%, 29%, and 20%, respectively. Our comparable findings of mean reductions in $FEV_{1.0}$ and FVC of 26% and 27%, respectively, imply that functionally near complete paralysis of the ipsilateral hemidiaphragm occurred in every patient 5 min after interscalene block injection. These previous studies were presumably done in the upright position, which is less sensitive for diagnosing diaphragmatic paresis because of the weight of the abdominal contents that act to pull the flaccid paretic hemidiaphragm downward (11). Our investigation was done on patients in the supine position, in which the subject's abdominal contents push the paretic diaphragm in a cephalad direction and therefore may increase the degree of pulmonary dysfunction by means of a diminution in vital capacity. We have since found in a separate study of 20 patients that a small further decrement in pulmonary function occurred when follow-up measurements were made after the 5-min point following interscalene local anesthetic injection (12).

We believe that the major mechanism responsible for these measured decreases in spirometric volumes is diminished inspiratory strength resulting from diaphragmatic paresis. This leads to an inability to fully inspire to total lung capacity and a resultant decrease in FVC, as well as in the other volumes and flows that constitute routine pulmonary function testing. Any reduction in maximum inspiratory muscle effort will directly translate to at least an equal diminution in measured expiratory volume. Maximum expiratory flows at any given volume will also decrease, as airflow from the lung is a single-valued function of lung volume. However, in addition to its role as the major muscle of inspiration, the diaphragm may also have some degree of expiratory function (13). To quantify any reduction in expiratory function that occurred during hemidiaphragmatic paresis, data were analyzed by volume-indexing the flow-volume measurements (see Methods). Measuring any true loss in expiratory function is important in increasing our understanding of how this anesthetic affects the patient's ability to cough perioperatively. The validity of the analysis used depends on there being no decrease in RV. Data from previous investigations showed *increases* in RV with unilateral hemidiaphragmatic paralysis (6,14). However, although we do not believe that RV decreased in our patients 5 min after interscalene block, we did not use gas dilution or plethysmographic techniques to evaluate this. If, in fact, an increase in RV, as reported previously, occurred at this point, any measured reduction in PEFR that we found by volume-indexing would indeed underestimate the actual reduction. In any event, the patient under interscalene anesthesia has a decreased ability to deep breathe, cough, and clear secretions. The block may also interfere with the patient's ability to perform effective incentive spirometry in the immediate postoperative period.

Reports of altered chest wall mechanics during complete pathological paresis of both hemidiaphragms have been published previously (11,14,15). In these studies, normal and deep inspiration (the *active* part of normal breathing) were characterized by increased inspiratory upper rib cage expansion and abdominal paradoxical (inward) motion as illustrated in Figure 3. Therefore, in addition to causing large measurable decreases in standard pulmonary function tests, phrenic nerve paresis changes the actual mechanics of respiration. During interscalene block, we found consistent similarly characterized distortions in chest wall mechanics, but with abdominal paradoxical motion *only* on the side of the block.

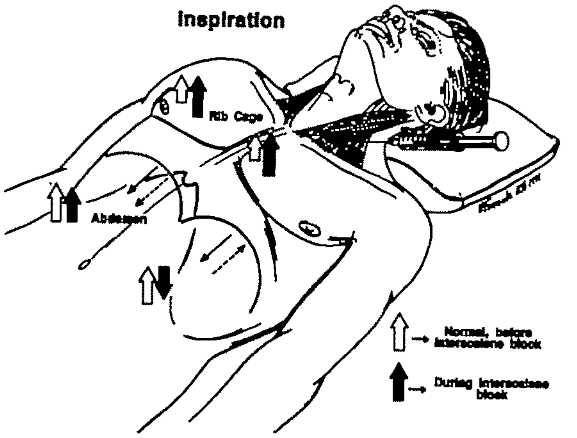

Figure 3. Illustration of typical changes in chest wall motion measured by magnetometry during interscalene anesthesia. The ipsilateral hemiabdomen no longer expanded, contracting instead with tidal inspiration 10 min after interscalene brachial plexus injection of mepivacaine.

Underlying lung expansion follows regional chest wall expansion. As the lower rib cage has been shown to act in the same manner and move in conjunction with the abdomen (15), unilateral hemidiaphragmatic paresis may lead to decreased lower lung expansion on the side of the block. In fact, decreased regional ventilation has been measured on the affected side in unilateral hemidiaphragmatic paralysis (6). Thus, chest wall distortion during hemidiaphragmatic paresis may lead to regional atelectasis (2).

Paralysis or severe weakness of the diaphragm does not by itself lead to respiratory failure in the completely healthy patient (17). However, normal respiration depends on timed coordination between the diaphragm and the other respiratory muscles (9,16,17). The activity of the compensatory muscles (intercostals and accessory) has been shown to decrease during rapid eye movement sleep, and ventilation is reduced during sleep in dogs with acute diaphragmatic paralysis (19). Interscalene block is often done in conjunction with general anesthesia or sedation, and the resulting inhibition of intercostal and accessory muscles during sleep or sedation may be detrimental to lung expansion and gas exchange. For this reason, we administer oxygen to all of our patients receiving this form of regional anesthesia.

In patients who are dependent on intact diaphragmatic function and cannot recruit intercostal or accessory muscles to effect, as in ankylosing spondylitis, ventilatory failure may be precipitated by hemidiaphragmatic paresis (20). The fact that large reductions in pulmonary function tests were measured in our two patients with preexisting pulmonary disease has implications for determining anesthetic choice in patients with moderate or severe obstructive lung disease. Patients unable to tolerate a potential 25% reduction in pulmonary function because of preexisting disease may benefit from another anesthetic technique, either general anesthesia with controlled ventilation or, if possible, axillary block as this regional anesthetic does not paralyze the diaphragm (2). Although infrequent, when a patient does develop dyspnea after interscalene injection, treatment should include reassurance, administration of oxygen, and placement of the patient in the sitting position if possible to optimize diaphragmatic mechanics. If these measures fail, intermittent positive pressure by mask or controlled ventilation should be instituted.

There are a few potential weaknesses concerning our study protocol, and data interpretation must be made while keeping these in mind. First, our measurements were made only 5 min after the block. This is a bit premature for complete major nerve blockade to occur, which may take 10–20 min for maximum local anesthetic effect. We have since made sequential measurements on more than 60 patients for a study period of 30 min after interscalene block and have found that only a small further decrement in pulmonary function occurred (12). We were indeed surprised to find that paresis of the phrenic nerve with the measured degree of pulmonary dysfunction occurred so rapidly after interscalene block. We have since found that all pulmonary function changes are essentially complete by 15 min (12). If respiratory insufficiency does occur, it should therefore be seen early, while the patient is under the care of the anesthetist. Second, we used a 45-mL dose of local anesthetic. There is some evidence that when using a single-injection technique, large volumes of local anesthetic produce a more reliable block than smaller volumes (21). We have found in a more recent study that a 20-mL dose produced no significant difference in onset or degree of pulmonary dysfunction when compared in a randomized fashion with a 45-mL dose (12). Finally, interscalene block may also cause paresis of the accessory muscles of inspiration and of the scalene muscles that are classified as inspiratory muscles, and this may have contributed to the pulmonary function decreases measured.

In conclusion, interscalene block caused large reductions in standard pulmonary function tests in every patient studied. The reductions in pulmonary function were similar in magnitude to those associated with complete unilateral phrenic nerve paralysis published previously. This anesthetic technique separately reduces inspiratory and expiratory abilities. On the basis of altered regional chest wall expansion, interscalene block may lead to variations in ventilation distribution, regional expiratory flows during cough, and diminished lung expansion. Each of these factors could lead to postoperative atelectasis or other pulmonary morbidity, especially if long-acting local anesthetic agents or continuous infusions of local anesthetic are used for postoperative analgesia.

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Role of Afferent Neural Input in Regression of Sensory Paralysis During Epidural Analgesia

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This study was designed to determine the role of the afferent peripheral neural input in the regression of sensory analgesia during epidural analgesia. Eighteen patients who underwent minor obstetric or gynecologic surgery under lumbar epidural analgesia with lidocaine were divided into three groups. Group A received electrical single twitch stimulation at the spinal nerve dermatome one segment rostrad of the proximal extent of sensory paralysis. Group B received electrical twitch stimulation at the anterior crural region where nerve block may have been most profound in this study. Group C was assigned as a control and did not receive any stimulation. The patients received the stimulation for 60 min (i.e., from 80 to 140 min after the epidural injection). The range of sensory analgesia at 140 min was compared with that at 80 min. The regression of sensory analgesia in group B or C was 1 ± 0 (mean ± SD) spinal nerve segments, but in group A it was 5 ± 1, which was significantly ($P < 0.0025$) larger than the others. We conclude that the afferent peripheral neural input to a spinal segment where the nerve block is incomplete may accelerate the regression of sensory analgesia from epidural analgesia.

(Anesth Analg 1992;74:358–61)

Regression of sensory analgesia or acute tolerance (tachyphylaxis) can occur during epidural analgesia. "Tachyphylaxis" is the term used for the continuous decline in effect, manifested as either a diminished response to a standardized dose of local anesthetic or an increased dose requirement to maintain a constant analgesic response. Although tachyphylaxis is a well-known problem, its pathogenesis remains to be clarified.

In 1987, Bigler et al. (1) proposed a new hypothesis that tachyphylaxis is due to a relative reduction in the efficiency of the neurogenic block by local anesthetics secondary to posttraumatic increases in afferent neurogenic input, thereby overriding the neurogenic block. This hypothesis was based on experimental studies showing postinjury hypersensitivity or a finding of a lower threshold in nociceptors and increased excitability both peripherally and in the spinal cord after peripheral trauma (2). Bigler et al. attributed the reduced extent of sensory analgesia to increased afferent input that may override the blocking effect of epidural analgesia at its weakest point; that point may be most rostrad, thereby primarily reducing the proximal extent of sensory analgesia.

Clinical studies performed since the proposal of Bigler et al. have found new evidence concerning the pharmacokinetics of epidurally administered local anesthetics and the duration of analgesia in acute or chronic pain (3–7). However, no studies have been performed to test the validity of their hypothesis. Therefore, we designed a study to determine the role of the afferent peripheral neural input in the regression of sensory analgesia during epidural analgesia.

Methods

The study was performed on 18 patients for whom prolonged epidural analgesia may not be advantageous. The studied patients underwent minor obstetric or gynecologic surgery, such as dilation and curettage or cone biopsy of the cervix. The study was approved by Ethics Committee for Medical Research of Kochi Medical School. Informed consent was obtained from each patient, and no complications or side effects were seen.

The epidural catheter was inserted 5 cm upward from L4-5, and 2% lidocaine containing 1:200,000 epinephrine was injected together with 0.1 mg of fentanyl through it. To obtain complete sensory analgesia from T-10 to S-5, the volume of 2% lidocaine was adjusted according to the patient's age, i.e., 17 mL for 20–29 yr, 16 mL for 30–39 yr, and 15 mL for 40–49 yr. The range of sensory analgesia was deter-

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mined by the pinprick method. Surgery was started 20–30 min after the epidural injection.

After surgery, the patients were randomly divided into three groups (groups A, B, and C). The patients in groups A and B received electrical twitch stimulation. In group A, two electrocardiographic electrodes (Red Dot, 3M Medical-Surgical Division) were placed on the left side of the chest or abdominal wall at the spinal nerve dermatome, one segment rostrad of the proximal extent of complete sensory paralysis. The first electrode was placed along the mammillary line, and the second one was placed 3 cm lateral of the first. In group B two electrocardiographic electrodes, 3 cm from each other, were placed at the middle of the left anterior crural region along the anterior tibial muscle bundle. The patients in group C were assigned as controls and did not receive stimulation.

The electrical twitch stimulus was generated with a Myotest RT5-3s MKII, BioMeter: output amplitude, 300 V into the open circuit, 150 V into 2500-Ω load; output current, variable from levels 0 to 10, or 0 to maximum 60 mA; output pulse shape, rectangular, 0.2 ms wide. The frequency of the twitch was 1 Hz. Group A patients were allowed to adjust the output current by themselves to a maximum level at which they were able to tolerate the stimulus without feeling any discomfort or pain. In group B, the output current level of the generator was set at 8/10 of the maximum. The patients received the stimulation for 60 min, i.e., from 80 to 140 min after the epidural injection. The range of sensory analgesia at 140 min was compared with that at 80 min.

The results were expressed as the mean ± SD. Two-way (time and group) analysis of variance with repeated measurements was used to assess the mean change in the extent of sensory analgesia. Differences among groups were tested by the Duncan's test. P-values of less than 0.05 were considered significant.

Results

There were no significant differences in the age and body weight or the proximal extent of sensory analgesia at 80 min among the three patient groups (Table 1). Group A patients received an output current level ranging from 7/10 to 8/10 of the maximum, which caused significant ($P < 0.0025$) regression of sensory analgesia at 140 min (Figure 1). The regression of sensory analgesia occurred bilaterally and symmetrically. There was no significant difference between groups B and C in the regression of sensory analgesia at 140 min. The distal extent of sensory analgesia was S-5 during the study period in all patients.

Table 1. The Physical Status of Patients and Proximal Extent of Sensory Analgesia

Group	Age (yr)	BW (kg)	Level of analgesia[a] 80 min	Level of analgesia[a] 140 min
A	32 ± 2	50 ± 3	T-10 ± 1	L-3 ± 2[b]
B	31 ± 5	48 ± 3	T-10 ± 1	T-11 ± 1
C	30 ± 3	49 ± 3	T-10 ± 1	T-11 ± 0

BW, body weight.
Values are mean ± SD.
[a] After epidural injection of anesthetic.
[b] $P < 0.0025$ vs groups B and C.

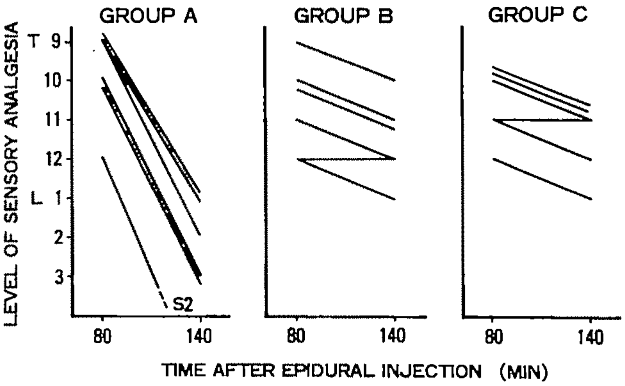

Figure 1. The regression of sensory analgesia in groups A, B, and C during the study period. The level of sensory analgesia at 140 min in group A is significantly ($P < 0.0025$) lower than in groups B and C.

Discussion

In regional analgesia, pain relief and operative duration are not synonymous, and the operative duration that regional analgesia permits is usually less than the duration of pain relief afforded by that regional analgesia (8). We commonly learn by experience that the duration of analgesia is extremely short when the state of surgical analgesia is incomplete. For example, when surgical stimulation is given to an incompletely blocked area, the patient may recognize the stimulation as being touched for a moment, but the sensation may quickly change to pain. This suggests that surgical stimulation may reduce the efficacy and duration of analgesia.

The purpose of the electric stimulation in this study was to determine the effect of an innocuous stimulus on the regression of sensory analgesia when the stimulus is given to the spinal cord segment, where the quality of nerve block is either incomplete or complete. The stimulation in group A was given to the skin dermatome, one segment rostrad of the proximal extent of complete sensory paralysis as determined by the pinprick method, where the quality of nerve block was assumed to be incomplete. The stimulation in group B was given to the skin dermatome, where the nerve block may have been most profound in this study: the sensory dermatome of the anterior crural region is L-5, and the nerve supply of the anterior tibial muscle is L4-5 and S-1.

The results in group B showed that an innocuous stimulus given to an area of profound nerve block with complete sensory paralysis does not influence the regression of sensory analgesia during epidural analgesia by lidocaine. The results in group A, on the contrary, suggested that peripheral nerve stimulation given to the spinal cord segments where the nerve block by epidural lidocaine is incomplete may accelerate regression of the sensory analgesia even when the sensory input is not intense enough to cause a pain sensation.

Perhaps the rapid regression of sensory analgesia in group A was due to the so-called postinjury hypersensitivity. Postinjury hypersensitivity, i.e., an increased sensitivity to noxious stimuli and pain after innocuous stimuli, has been produced by noxious skin stimuli that are sufficiently intense to produce tissue injury in experimental studies (2,9,10). The skin stimulus in this study was not so intense as to produce tissue injury. Thus, the cause of the rapid regression in sensory analgesia observed in group A may not be due to classical postinjury hypersensitivity. However, the mechanism behind the rapid regression of sensory analgesia may be similar to postinjury hypersensitivity: the stimulation may have produced an increase in the excitability of the central nervous system, thereby producing rapid regression of sensory analgesia.

In the management of continuous epidural analgesia, the timing of successive doses is important; a refill dose given more than 10 min after disappearance of the preceding area of analgesia may result in significant attenuation of the nerve blocking effect (11). This suggests that increased peripheral and central nervous system excitability may contribute importantly to the occurrence of tachyphylaxis. Thus, our results strongly support the hypothesis proposed by Bigler et al. (1) in terms of the effect of peripheral nerve stimulation on the reduction in the efficacy of the neurogenic block achieved by a local anesthetic. Even innocuous stimuli caused rapid regression of sensory analgesia in this study. Thus, noxious stimuli derived from surgery can be an important cause of reduced efficacy of the neurogenic block during epidural analgesia when the stimuli are given to spinal segments where the nerve block is incomplete.

Mogensen et al. (7) reported that there was no change in the rate of blood elimination in lidocaine tachyphylaxis. However, they also found that the rate of vascular absorption of anesthetic from the epidural space may contribute importantly to tachyphylaxis associated with repeated epidural injection of bupivacaine (5). Thus, increased clearance of epidural lidocaine has not been ruled out as a cause of regression of analgesia.

As the metabolic rate of an organ increases with activity, local vasodilation and an increased blood flow usually result. This is also true in neural tissues. An increase in the nerve activity increases the neural tissue blood flow (12,13). Lidocaine applied topically to a nerve, on the contrary, reduces nerve blood flow, which can be reversed by washing off the anesthetic (14). It is possible, therefore, that changes in the neural activity may influence the blood elimination rate of local anesthetic in the neural tissue.

Peripheral nerves consist of either efferent or afferent neurons, and blood vessels of intrinsic circulation, which are surrounded by a perineurium to form a neuronal fascicle. The fascicles and blood vessels of the extrinsic circulation are covered with epineurium. Activation of unblocked neurons may cause vasodilation of the intrinsic blood vessels and increase the blood flow of the intrinsic and extrinsic circulation, which facilitates the blood removal of local anesthetic. This may also be true in other neural tissues, including the spinal cord and its root. Thus, electrical stimulation in group A may have activated unblocked neurons, such as those conducting touch sensations, thereby enhancing clearance of the lidocaine from the neural tissue. The resultant decreased local concentration of the anesthetic may have facilitated the recovery of blocked neurons, such as those conducting pain sensations. It is possible, therefore, that increased blood elimination of local anesthetic from neural tissues may be one of the causes of accelerated regression of analgesia.

Epidural morphine administered with bupivacaine is reported to prevent tachyphylaxis (15). Addition of fentanyl to bupivacaine increased the duration and quality of analgesia in two studies (16,17), but neither study addressed its effect on tachyphylaxis. We evaluated the effect of fentanyl on the regression of sensory analgesia in a separate study by conducting epidural analgesia with a lidocaine solution not containing fentanyl, but fentanyl did not apparently modify the effect of the afferent neural input on the decay of analgesia.

In conclusion, we demonstrated that peripheral nerve stimulation given to spinal cord segments with complete nerve block by a local anesthetic does not influence the regression of the sensory analgesia. However, nerve stimulation given to a spinal segment with incomplete nerve block may accelerate the regression of the sensory analgesia. Therefore, during epidural analgesia with lidocaine, we should be aware of the potential for innocuous stimuli to exert an important influence on the regression of the sensory analgesia when the nerve block is incomplete.

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Differential Analgesic Effects of Low-Dose Epidural Morphine and Morphine-Bupivacaine at Rest and During Mobilization After Major Abdominal Surgery

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In a double-blind, randomized study, epidural infusions of low-dose morphine (0.2 mg/h) combined with low-dose bupivacaine (10 mg/h) were compared with epidural infusions of low-dose morphine (0.2 mg/h) alone for postoperative analgesia at rest and during mobilization and cough in 24 patients after elective major abdominal surgery. All patients in addition received systemic piroxicam (20 mg daily). No significant differences were observed between the groups at any assessment of pain at rest ($P > 0.05$), whereas pain in the morphine/bupivacaine group was significantly reduced during mobilization from the supine into the sitting position 12 and 30 h after surgical incision and during cough 8, 12, and 30 h after surgical incision ($P < 0.05$). We conclude, that low-dose epidural bupivacaine potentiates postoperative low-dose epidural morphine analgesia during mobilization and cough. Evaluation of postoperative analgesic regimens should include assessment of pain during various activities as different analgesics may have differential effects on pain at rest and during mobilization.

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The combination of epidural local anesthetic and opioid has improved pain relief compared with administration of epidural local anesthetic alone after abdominal (1–4) and thoracic (5) surgery and cesarean delivery (6). However, results from studies comparing epidural local anesthetic/opioid mixtures with epidural opioids alone are contradictory (1,2,5–10), and in most studies, no benefit from the addition of local anesthetic has been demonstrated (1,5,8–10).

The effects of epidural opioids and local anesthetics on pain during ambulation has not been systematically investigated, but data from studies on cancer pain suggest that epidural morphine may have differential effects on different pain qualities (11). We speculated, therefore, whether a differential effect of morphine compared with a combination of morphine and bupivacaine could be demonstrated on postoperative pain at rest and during various activities.

The aim of this study was to investigate the influence of low-dose bupivacaine as an adjunct to continuous epidural infusion of low-dose morphine on postoperative pain at rest and during mobilization and cough after major abdominal surgery.

Methods

Twenty-four patients scheduled for elective major abdominal surgery were included in the study. Informed consent was obtained from all patients, and the study was approved by the local Ethics Committee.

On the evening before surgery and again 1 h before surgery, the patients received piroxicam (40 mg orally). On the following 2 days 20 mg of piroxicam was administered rectally every morning. As premedication, patients received 5–15 mg of diazepam by mouth 1 h before operation.

Before induction of general anesthesia an epidural catheter (Portex 18-gauge) was inserted between T-9 and T-12, depending on the site of operation, and was tested with 2 mL of bupivacaine (7.5 mg/mL). Seven milliliters of plain bupivacaine (7.5 mg/mL) plus 2 mg of morphine was then injected epidurally,

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followed by continuous epidural infusion of a mixture of bupivacaine (7.5 mg/mL) and morphine (0.05 mg/mL), 4 mL/h until the end of operation.

General anesthesia was induced with thiopentone (2–5 mg/kg) and fentanyl (0.1–0.2 mg); after precurarization with pancuronium (0.01 mg/kg), succinylcholine (1.5 mg/kg) was used to facilitate orotracheal intubation. General anesthesia was maintained with N_2O/O_2 (2:1) and enflurane (0.25%–1%). Pancuronium or atracurium was used to supplement neuromuscular blockade if necessary.

At the end of surgery, but before general anesthesia was withdrawn, patients were randomized to receive either a continuous epidural infusion of morphine (0.05 mg/mL), (group M, 4 mL/h), or a continuous epidural infusion of a mixture of morphine (0.05 mg/mL) and bupivacaine (2.5 mg/mL), (group M + B, 4 mL/h), continued for 48 h postoperatively using a Pharmacia Deltec pump. Postoperatively, 5 mg of morphine (IV or IM) with no limitations on frequency was given exclusively if requested by the patient. All patients remained in the intensive care unit for at least 12 h as recommended by the Danish National Health Service.

Pain scores on a visual analogue scale (0 mm = no pain, 100 mm worst pain imaginable) at rest, during mobilization from the supine into the sitting position, and during cough and levels of sensory analgesia (pinprick bilaterally) and motor blockade on a 0–3 point scale (Bromage: 0 = no paralysis, 3 = total paralysis) were assessed 4, 8, 12, 24, 30, and 48 h after surgical incision by an investigator blinded to the treatment groups.

Binomial data were evaluated with Fisher's exact test. Morphine consumption and pain score between groups at each time point were evaluated with the Mann-Whitney rank-sum test for unpaired data. $P < 0.05$ was considered significant.

Results

Groups M and M + B were not significantly different with regard to age, sex, height, body weight, and duration of surgery (Table 1), and whether surgery was in the upper or lower abdomen (Table 2). One patient in group M and one patient in group M + B underwent another operation 8 h (postoperative bleeding) and 32 h (necrotic stoma) after surgery, respectively, and data from these patients are only included until reoperation.

Three patients in group M received additional morphine 0–24 h after surgical incision (20, 6, and 18 mg, respectively), and four patients received additional morphine 24–48 h after surgical incision (5, 35, 60, and 7 mg, respectively), whereas only one patient in the M + B group received a total amount of 7.5 and 27.5 mg of additional morphine 0–24 and 24–48 h after surgical incision ($P > 0.05$).

Table 1. Demographic Data

	Epidural morphine (*n* = 12)	Epidural morphine + bupivacaine (*n* = 12)
Age (yr)	66 ± 4	62 ± 5
Sex (male/female)	8/4	3/9
Height (cm)	168 ± 4	171 ± 3
Weight (kg)	70 ± 4	70 ± 5
Duration of surgery (min)	152 ± 15	176 ± 16

Values are mean ± SEM.
$P > 0.05$ for all variables.

Table 2. Surgical Procedures

	Epidural morphine (*n* = 12)	Epidural morphine + bupivacaine (*n* = 12)
Rectal amputation	—	2
Rectosigmoid resection	6	4
Hemicolectomy	1	3
Cholecystectomy	2	3
Gastric resection	2	—
Jejunal resection	1	—

No significant differences in pain scores were observed between the two groups at rest, during mobilization from the supine into the sitting position, or during cough 4 h after surgical incision. The combined epidural blockade with bupivacaine and morphine, initiated before surgery, was still effective during this period as evaluated by pinprick in both groups (Figure 1). After this time, when regression of sensory blockade to pinprick in group M was evident (Figure 1), no significant differences were observed between the groups at any assessment of pain at rest ($P > 0.05$), whereas a significant difference was observed during mobilization from the supine into the sitting position 12 and 30 h after surgical incision and during cough 8, 12, and 30 h after surgical incision ($P < 0.05$) (Figure 2).

No sensory blockade to pinprick was detectable in group M patients 24 h after surgical incision except for two patients with residual blockade from T-4 to T-6 and T-3 to L-2 48 h after surgery, respectively. Sensory blockade to pinprick from mean T-6 to T-12 was still present in group M + B patients 48 h after surgical incision (Figure 1). No motor blockade was demonstrable in group M or group M + B 8 and 12 h after surgical incision, respectively, in any patient. No cardiovascular or respiratory complications requiring treatment were observed during the study.

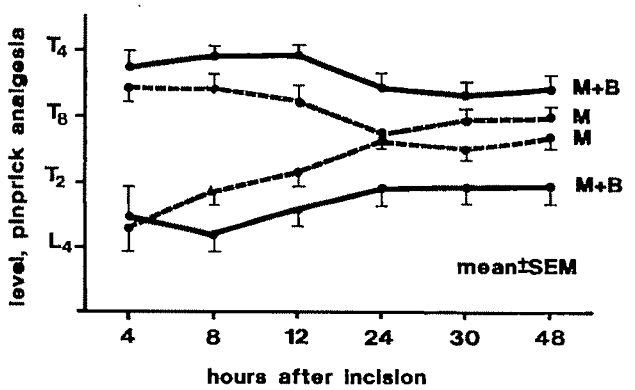

Figure 1. Sensory analgesia to pinprick after intraoperative combined epidural and general anesthesia in patients receiving continuous epidural infusion of 0.05 mg/mL of morphine, 4 mL/h (*dashed line*, M), or continuous epidural infusion of 0.05 mg/mL of morphine + 2.5 mg/mL of bupivacaine, 4 mL/h (*solid line*, M + B), mean ± SEM. Level of insertion of epidural catheter T-8.8 ± 0.3 and T-8.8 ± 0.4 in the morphine and morphine + bupivacaine group, respectively (mean ± SEM).

Discussion

Continuous epidural administration of local anesthetics may be a powerful tool in pain alleviation during the postoperative period, but unpredictable instability (12,13) as well as tachyphylaxis (14,15) may compromise maintenance of analgesia, with insufficient control of pain at rest and during mobilization. In experimental studies, local anesthetics have been demonstrated to potentiate spinal morphine antinociception even at doses at which the drugs by themselves had no or little effect (16). In clinical studies, the combination of epidural local anesthetics with opioids has been demonstrated to maintain sensory analgesia (3,4) and to improve pain relief after abdominal (1–4), thoracic (5), and gynecologic (6) surgery compared with epidural local anesthetics alone, thus confirming the experimental data (16).

In contrast, results from studies comparing epidural local anesthetic/opioid mixtures with epidural opioid alone are contradictory (1,2,5–10), as all but two studies with administration of high-dose epidural local anesthetic (2,7) showed no advantageous effect of adding local anesthetic to epidural opioid. In none of these studies, however, was pain assessed during various activities (1,2,5–10).

The afferent nociceptive input from the operative field may differ during rest and mobilization, but the effect of epidural opioids and local anesthetics during ambulation has not been systematically investigated. In our study, we observed no significant difference between pain scores at rest during a continuous epidural infusion of morphine as compared with morphine plus bupivacaine, whereas pain was more pronounced ($P < 0.05$) during mobilization and cough in patients who received epidural morphine only.

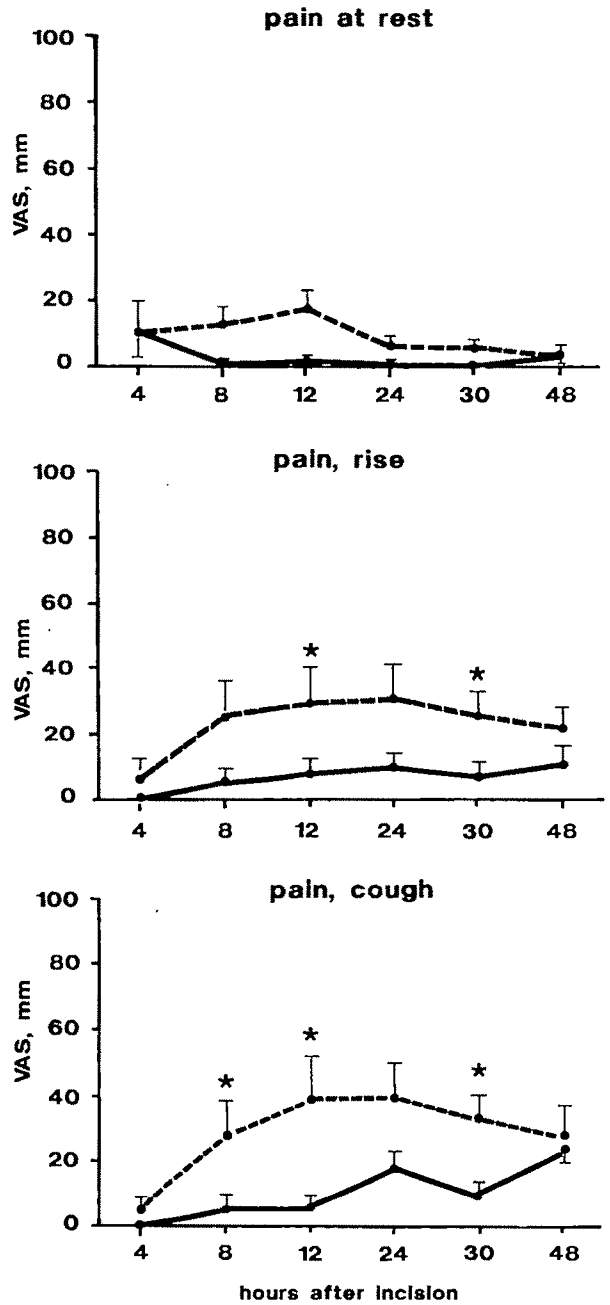

Figure 2. Pain at rest, during mobilization from the supine into the sitting position, and during cough in patients receiving continuous epidural infusion of 0.05 mg/mL of morphine, 4 mL/h (*dashed line*), or continuous epidural infusion of 0.05 mg/mL of morphine + 2.5 mg/mL of bupivacaine, 4 mL/h (*solid line*), mean ± SEM. *$P < 0.05$.

Both groups of patients in our study received an intraoperative epidural blockade with bupivacaine and morphine, as preemptive neural blockade has been proposed to reduce postoperative pain (17). Thus, the differences in postoperative pain between the groups observed in our study cannot be related to differences in the extent of post injury-pain hyperalgesia induced by the surgical trauma.

As administration of nonsteroidal antiinflammatory drugs has been demonstrated to reduce pain and systemic opioid requirements after major surgery (18), both groups of patients in our study received piroxicam in the perioperative period. Although an additive or synergistic effect of nonsteroidal antiinflammatory drugs combined with epidural opioid or opioid/local anesthetic has not been documented, there is no reason to believe that the addition of nonsteroidal antiinflammatory drugs should favor the combination of epidural morphine and bupivacaine more than epidural morphine alone.

Whether the addition of low-dose local anesthetic to continuous low-dose opioid may increase side effects or morbidity was not addressed in our study and remains to be settled. In three studies in patients after abdominal surgery (1), thoracotomy (5), and orthopedic surgery (9), no differences in side effects were found. In the study by Badner and coworkers (9), significant hypotension and respiratory depression developed in one patient receiving a combination of low-dose epidural fentanyl and bupivacaine. It is not clear, however, whether this was due to the addition of bupivacaine, as severe respiratory depression has been demonstrated after epidural administration of fentanyl alone (19,20).

In conclusion, in a double-blind, randomized study, low-dose bupivacaine was demonstrated to improve postoperative epidural morphine analgesia during mobilization from the supine into the sitting position and during cough in patients after major abdominal surgery, whereas no significant difference was observed when pain was assessed at rest. Comparison of different postoperative analgesic regimens should include assessment of pain during various activities, as different analgesic methods may have differential effects on pain at rest and during mobilization.

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Systemic Piroxicam as an Adjunct to Combined Epidural Bupivacaine and Morphine for Postoperative Pain Relief—A Double-Blind Study

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In a randomized, double-blind, placebo-controlled trial, we assessed the value of adding rectal piroxicam to a low-dose epidural regimen for postoperative pain relief. Forty-four patients scheduled for major upper abdominal surgery during combined thoracic epidural (bupivacaine + morphine) and general anesthesia were studied. Postoperative analgesia was achieved by using epidural bupivacaine (10 mg/h) plus morphine (0.2 mg/h) for 72 h. In addition, the patients randomly received a placebo or rectal piroxicam (40 mg 12 h before surgery, 20 mg with premedication, and 20 mg every 24 h for 72 h). Pain was evaluated every 4 h at rest, during coughing on demand, and during mobilization. The sensory level of analgesia was evaluated by pinprick. We found no significant difference between piroxicam and placebo with regard to postoperative pain scores or need for supplementary analgesics. Thus, we were unable to demonstrate enhanced analgesia by adding piroxicam to an otherwise very effective low-dose epidural bupivacaine and morphine treatment after upper abdominal surgery.

(Anesth Analg 1992;74:366–70)

The standard of postoperative pain treatment is poor in daily clinical practice (1). Systemic opioids may provide variable analgesia but not total pain relief without side effects. Epidural administration of local anesthetics and opioids, alone or in combination, provides improved pain relief but also presents the risk of side effects (2–7).

We previously emphasized that total postoperative pain relief cannot be achieved by a single drug or method without major expenditure on equipment and/or surveillance systems or without significant side effects (8), and therefore recommended combined analgesic regimens (balanced analgesia) or a multimodal approach to the treatment of postoperative pain (8,9). Nonsteroidal antiinflammatory drugs (NSAIDs) reduce pain after surgery (10–15). Their mechanism of action is different from local anesthetics and opioids, as NSAIDs inhibit the synthesis and release of prostaglandins at the site of the surgical trauma, thereby reducing the hyperalgesia caused by prostaglandin-mediated sensitization of the nociceptors to mechanical or chemical stimulation after tissue injury (16). The aim of this study was to evaluate the effect of adding an NSAID (piroxicam) to a low-dose regimen of continuous epidural local anesthetics and morphine on pain relief after major upper abdominal surgery.

Methods

This was a randomized, placebo-controlled, double-blind trial designed and consistent with the Helsinki II Declaration. The study was approved by the regional ethical committee and the Danish Health Service, and informed consent was obtained from each patient. The study was designed to include 40 patients, therefore excluded patients were replaced.

Forty-four patients scheduled for major upper abdominal surgery were premedicated with diazepam (0.2 mg/kg) and given general anesthesia induced with fentanyl (0.2 mg) and thiopental (3–5 mg/kg); after precurarization with pancuronium (0.01 mg/kg), succinylcholine (1.5 mg/kg) was used to facilitate orotracheal intubation. General anesthesia was maintained with N_2O/O_2 (2:1), enflurane (0.5%–1.5%),

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and small amounts of pancuronium if necessary. An epidural catheter was inserted between T-7 and T-8 before induction of general anesthesia, and 9 mL of plain bupivacaine (0.5%) and 2 mg of morphine was used to produce epidural analgesia.

The postoperative pain treatment consisted of 4 mL/h of 0.25% epidural bupivacaine plus 0.2 mg/h of morphine initiated 30 min after the initial dose of bupivacaine and morphine and scheduled for 72 h. Drugs were delivered by a Pharmacia Deltec infusion pump. The patients were randomized double-blind to receive either piroxicam (Felden, 40 mg rectally 12 h before surgery, 20 mg rectally together with premedication, and 20 mg every 24 h for 72 h; group 1) or placebo suppositories (group 2). On request the patients received supplemental morphine (0.15 mg/kg) intramuscularly.

Pain was evaluated every 4 h when the patients at rest were asked to cough and during mobilization from the supine to sitting position in bed using a 10-cm visual analogue scale (VAS) and verbal rate scoring (0 = no pain, 1 = slight pain, 2 = moderate pain, 3 = severe pain, and 4 = unbearable pain). The sensory level of analgesia was evaluated by pinprick. There were no measurements between midnight and 8 AM. The evaluation was performed by the authors.

Results are expressed as median + range. The Mann-Whitney test for unpaired data was used to compare the two groups. As the trial design implied multiple within-person assessments of pain over time, the relevant statistical method is analysis of variance. Because of ordinal measurements, we used a corresponding nonparametric method (17) in which treatments were compared with the Mann-Whitney test for unpaired data disregarding time, but both the factor time and the interaction between time and treatment were assessed by Friedmann tests. $P < 0.05$ was considered as significant. The number of patients was chosen to insure $2\alpha = 0.05$ and $\beta = 0.05$ with an effect of 1.5 cm on the VAS score during cough. This gives approximately 20 patients in each group with a standard deviation on 1.2 cm. To indicate the statistical power of the trial, median difference and 95% confidence limits were calculated for the VAS scores during mobilization.

Results

Four patients were excluded from the study: two because of a nonfunctioning epidural catheter, one because the patient did not receive the piroxicam/placebo in the morning before surgery, and one with hypotension because of hypovolemia a few hours postoperatively. Thus, the study population comprised 40 patients.

Table 1. Clinical Data

	Epidural + piroxicam ($n = 20$)	Epidural + placebo ($n = 20$)	P
Age (yr)	55 (21–72)	57 (21–81)	NS
Weight (kg)	70 (50–119)	67 (46–91)	NS
Height (cm)	174 (155–192)	174 (160–182)	NS
Duration of surgery (min)	270 (80–330)	308 (150–780)	<0.05
Blood loss (mL)	300 (0–2000)	1060 (150–4000)	<0.05
Supplemental IM morphine (mg)			
Day 1	6.25 (0–60)	0 (0–40)	NS
Day 2	0 (0–20)	0 (0–30)	NS
Day 3	0 (0–25)	0 (0–10)	NS

IM, intramuscular; NS, not significant.
Values are median (range).

In group 1 the surgical procedures were vagotomy ($n = 5$), choledochojejunostomy ($n = 3$), cholecystectomy ($n = 3$), small bowel resection ($n = 2$), gastric resection ($n = 2$), pancreatectomy ($n = 2$), right hemicolectomy ($n = 2$), and hemihepatectomy ($n = 1$). The procedures in group 2 were pancreatectomy ($n = 7$), hemihepatectomy ($n = 5$), small bowel resection ($n = 2$), gastric resection ($n = 2$), vagotomy ($n = 1$), right hemicolectomy ($n = 1$), cholecystectomy ($n = 1$), and explorative laparotomy ($n = 1$).

There was no difference between age, weight, and height in the two groups (Table 1). There was a significantly longer duration of surgery and blood loss in the placebo-treated patients (Table 1). Median VAS and verbal rate scores at rest, during cough, and during mobilization are shown in Figure 1. No significant difference between the piroxicam group (1) and the placebo group (2) was found. Owing to the long duration of surgery, evaluation of the patients in group 2 during cough and mobilization could only be done in 11 patients before the 12th hour after induction of anesthesia. The daily supplemental intramuscular dose of morphine was similar in the two groups (Table 1).

The number of patients with severe pain (verbal rate > 2) or no pain (verbal rate = 0) experienced at each measurement during cough is shown in Figure 2. There was no statistical difference between the two groups.

The calculated risk of an error of the second kind to overlook a difference in VAS scores during cough between the two groups is shown in Figure 3. There appears to be no risk for having overlooked a clinically important positive treatment effect of piroxicam.

The sensory levels of analgesia are shown in Figure 4. There was a slight but significant decrease in sensory level of analgesia in both groups ($P < 0.05$). However, there was no difference between the groups ($P > 0.05$).

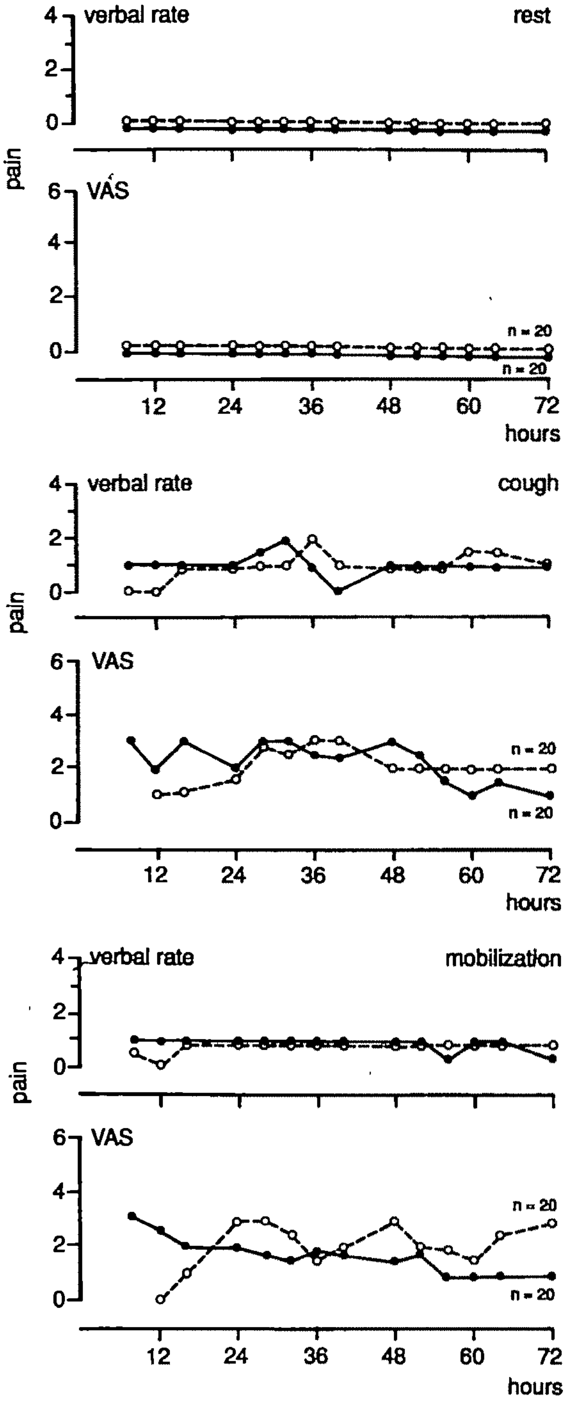

Figure 1. Median postoperative pain scores during rest (*top*), cough (*middle*), and mobilization (*bottom*) during continuous epidural bupivacaine (10 mg/h) plus morphine (0.2 mg/h) and systemic piroxicam (20 mg daily) (—) or placebo (—) after major upper abdominal surgery ($P > 0.3$).

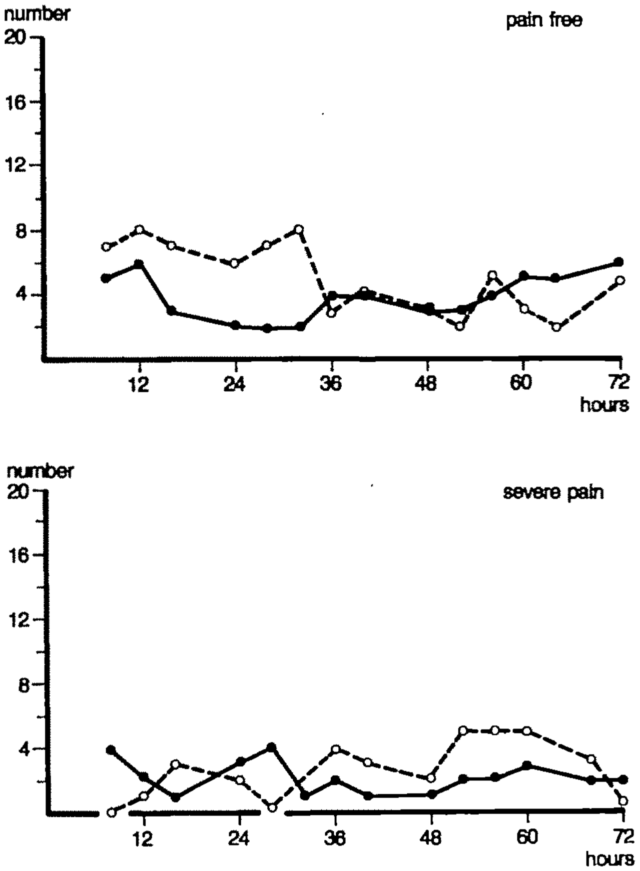

Figure 2. Number of patients pain free (verbal rate = 0) (*top*) and number of patients with severe pain (verbal rate ≥2) (*bottom*) during cough, during continuous epidural bupivacaine (10 mg/h) plus morphine (0.2 mg/h) and systemic piroxicam (20 mg daily) (—, $n = 20$) or placebo (—, $n = 20$) after major upper abdominal surgery ($P > 0.3$).

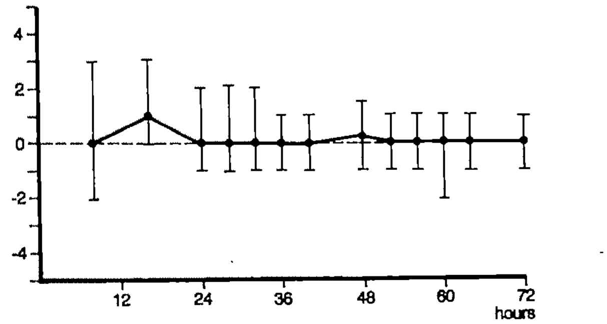

Figure 3. Median difference in VAS pain ([epidural + piroxicam] − [epidural + placebo]) during mobilization with 95% confidence limits.

Six patients required no urinary catheter during the study period. However, one of these needed an in and out catheterization. Eight patients had the catheter for 24 h, and seven patients had the urinary catheter for 48 h. One of these patients was recatheterized because of urinary retention. Nineteen patients required the urinary catheter during the 72-h study period owing to extensive surgery. No respiratory or bleeding complications indicating treatment were seen.

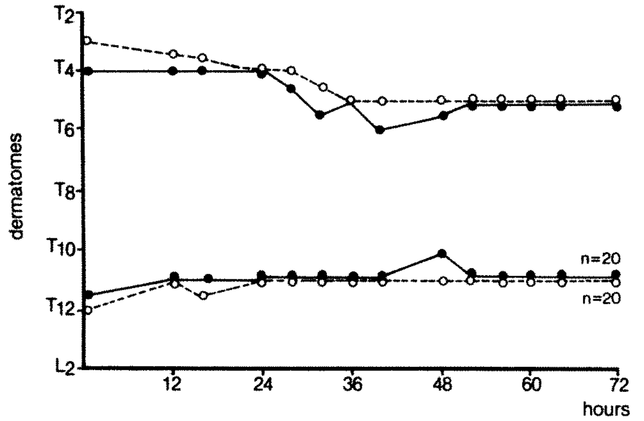

Figure 4. Median sensory level of analgesia (pinprick) during continuous epidural bupivacaine (10 mg/h) plus morphine (0.2 mg/h) and systemic piroxicam (20 mg daily) (—) or placebo (---) after major upper abdominal surgery ($P > 0.05$).

Discussion

Despite the major efforts in treatment of postoperative pain during recent years, it has still not been possible to prescribe a postoperative regimen after major upper abdominal surgery with total pain relief in all patients without the risk of side effects (8,9). Epidural local anesthetics in combination with morphine seems to be one of the most powerful methods, although not perfect, owing to the risk of respiratory depression, hypotension, and urinary retention with the higher doses needed to provide total pain relief (6,7). When the doses of morphine and local anesthetics are reduced, the number of side effects may decrease at the cost of inadequate pain relief. Therefore, there is a need for a new approach in the treatment of severe acute pain. We have previously advocated the term "balanced analgesia" (i.e., a combination of low doses of different analgesic drugs with different antinociceptive characteristics) (9).

As NSAIDs in most studies have shown a beneficial effect on postoperative pain after both abdominal and orthopedic surgery (10–15), we added rectally administered piroxicam to a low-dose continuous epidural local anesthetic plus morphine regimen to improve pain relief and at the same time hopefully to reduce side effects. Piroxicam, a long-acting NSAID, was chosen because it can be administered rectally with the same pharmacokinetic profile as seen after oral administration (18). The dose used in this study is equal to the dose used in previous studies (11,15).

However, we were unable to show enhanced analgesia by adding piroxicam (about 20 mg daily) to our epidural regimen. The epidural regimen (control) was very effective in itself with median pain scores at zero during rest, but 10%–20% of patients had pain (verbal rate > 2) during cough and mobilization.

The explanation for our inability to demonstrate an enhanced analgesic effect by piroxicam is not apparent from our study. One possibility could be an insufficient dose of piroxicam, but Sunshine et al. (14) in a study in surgery of less magnitude than ours did not show important differences between 20 and 40 mg with regard to pain relief. Furthermore, we used a preoperative initial dose of 40 mg 12 h before the operation. It is not likely that our negative results are due to an error of the second kind, as the median difference in analgesic effect is about zero between the two groups with very small 95% confidence limit (Figure 3). Although most studies have shown a positive effect of NSAID on postoperative pain and reduced requirements for opioids (10–15,19,20), the studies after laparotomy may be less positive than after other procedures (15). An additive/synergetic analgesic effect of adding piroxicam to opioid therapy has previously been demonstrated only in relatively minor laparotomy procedures or orthopedic surgery (14,21).

Our results may therefore be explained by the fact that the epidural regimen was very effective and that appearance of pain after major laparotomy cannot be further inhibited by adding piroxicam, at least not with the dose applied in this study. We are not able to differentiate the appearance of pain from the somatic vs the visceral system, which also may be of importance as NSAIDs probably are more effective in somatic acute pain. However, the pain during mobilization most probably comes from the abdominal wall, i.e., the somatic system.

In a previous study we have shown that the combination of indomethacin with epidural analgesia was extremely effective in alleviating postcholecystectomy pain (22). However, in that study the epidural dose of morphine was much higher (12 mg/24 h) compared with the present study, which makes it difficult to interprete the influence of indomethacin per se. Possible differential effects between different NSAIDs have not been evaluated (15). Regarding side effects, patients were observed on the general ward after an initial 12-h observation in the recovery room. We found no side effects except for one case of urinary retention. However, this does not allow any conclusion with regard to postoperative bladder dysfunction, as many patients had bladder catheterization for reasons other than the epidural pain treatment. Obviously, the relatively small size of our study did not allow conclusions on the risk of respiratory side effects, although they were not observed.

In conclusion, our double-blind study was not able to demonstrate an additional analgesic effect of piroxicam (20 mg daily) when combined with a low-dose epidural local anesthetic/morphine regimen after major abdominal surgery. However, the use of the multimodal approach (balanced analgesia) in the treatment of postoperative pain should be further evaluated, primarily during different surgical procedures, as should the possible differential efficacy profiles of different NSAIDs.

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Alkalinization of Mepivacaine for Axillary Block

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We examined the onset and distribution of sensory blockade, the onset of motor blockade, and venous mepivacaine concentrations after axillary block with 1.25% mepivacaine with and without bicarbonate. There were no statistically significant differences between the alkalinized and placebo groups with respect to distribution of analgesia or anesthesia, time to onset of analgesia, or time to onset of paresis. However, alkalinization significantly decreased the time to onset of anesthesia in the medial cutaneous nerve of the forearm, the median nerve, and the ulnar nerve, as well as the time to onset of paralysis. Concentrations of mepivacaine in venous blood did not differ significantly. We conclude that alkalinized mepivacaine offers the advantage of quicker onset of more profound blockade in several terminal nerve distributions.

(Anesth Analg 1992;74:371–4)

One means of hastening onset of regional blockade is to add sodium bicarbonate to commercially available hydrochloride salts of local anesthetics. Studies in epidural blockade have shown that alkalinization speeds onset of block (1–3), but results with alkalinization of local anesthetics in brachial plexus blockade have been conflicting (4–7). We examined the onset and distribution of sensory blockade, the onset of motor blockade, and venous concentrations of mepivacaine after axillary block with 1.25% mepivacaine with and without bicarbonate.

Methods

The protocol was approved by our institutional human investigation committee. We studied 26 adult patients scheduled for surgery on the hand or arm. We excluded patients with liver disease, kidney disease, seizure disorder, or extremes of weight (<50 kg or >100 kg) or age (>70 yr). Patients were randomly allocated to either the saline or alkalinized group.

Standard monitoring equipment was applied, and a 16-gauge venous cannula was placed in the contralateral arm. The axilla was prepared and draped in a sterile manner. Axillary block was performed with a 22-gauge short-bevel needle using an immobile needle technique. Residents performed all blocks under the direct supervision of one of the authors. The anesthetist attempted to transfix the axillary artery and disregarded any paresthesiae. Finger pressure was placed over the axillary artery distal to the site of injection. When the needle had passed through the posterior wall of the artery and aspiration tests were negative, a stopwatch was set (i.e., zero time for data collection), and 25 mL of local anesthetic was injected. An aspiration test was performed after injection of each 5 mL. The needle was withdrawn until it was no longer in the arterial lumen, and 25 mL of local anesthetic again was injected using the same technique.

Anesthetic solutions were mixed immediately before injection and consisted of 1.25% mepivacaine (equal volumes of 1% and 1.5% mepivacaine), plus 1 mL per 10 mL of solution of either 7.5% sodium bicarbonate or 0.9% NaCl. The mepivacaine concentration of the injected solutions was 1.13%.

The same blinded observer tested the onset of sensory blockade in the distribution of each of the terminal nerves of the brachial plexus every 2 min for 30 min in each patient. Analgesia was defined as a dulled sensation of pinprick, and anesthesia was defined as complete loss of ability to sense pinprick. Onset of motor blockade was tested at two sites. Proximal motor blockade was evaluated by ability to extend the forearm at the elbow. The patient subjectively reported the onset of paresis. Inability to extend the forearm against gravity constituted paralysis. Distal motor blockade was evaluated by the method of Winnie et al. (8). A pediatric blood pressure cuff was wrapped around the hand, and the

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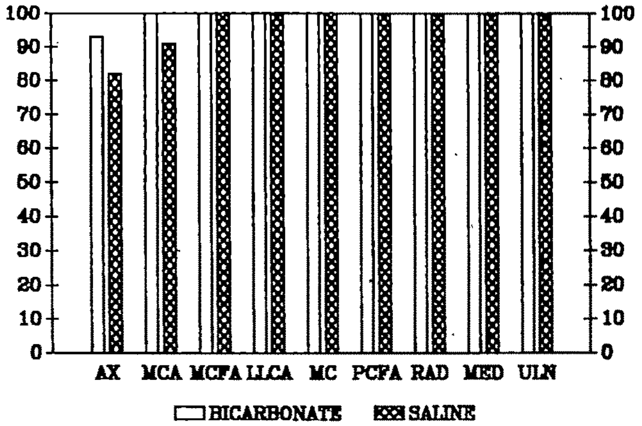

Figure 1. The percentage of patients in whom analgesia developed within the study period is plotted for each of the terminal nerves of the brachial plexus. AX, axillary; MCA, medial cutaneous of the arm; MCFA, medial cutaneous of the forearm; LLCA, lower lateral cutaneous of the arm; MC, musculocutaneous; PCFA, posterior cutaneous of the forearm; RAD, radial; MED, median; ULN, ulnar.

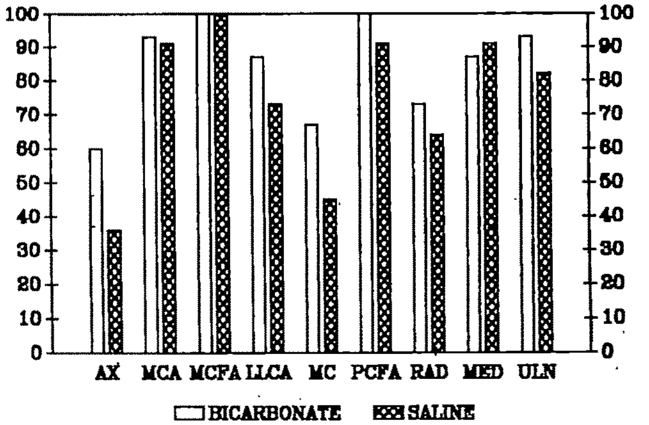

Figure 2. The percentage of patients in whom anesthesia developed during the study period is plotted for each of the terminal nerves of the brachial plexus.

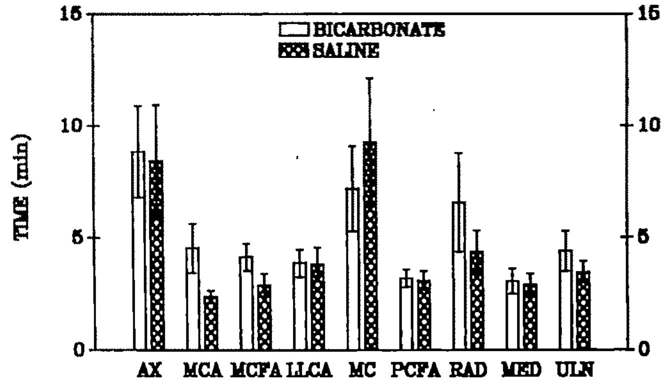

Figure 3. Mean time to onset of analgesia in minutes is plotted for each of the terminal nerves of the brachial plexus. Error bars are standard error of the mean.

pressure generated by maximal contraction was noted before nerve blockade. Inability to achieve this pressure after the block constituted paresis. Inability to move the fingers constituted paralysis.

Blood for determination of mepivacaine concentration was drawn from the venous cannula before the block and every 3 min for 30 min and then at 45, 60, 90, and 120 min after the block.

The intercostobrachial nerve was blocked by subcutaneous injection of 10 mL of 0.5% bupivacaine after the 30-min study period.

The pH of 1.25% mepivacaine solutions was determined by a pH meter. Sodium bicarbonate was added incrementally to the continuously stirred solution, and the resultant pH was noted.

Plasma concentration of mepivacaine was determined by gas chromatography (9).

Statistical analysis was by χ^2-analysis (comparison of frequency of successful blockade) or by analysis of variance. A *P* value of less than 0.05 was assigned statistical significance.

Results

Fifteen patients received alkalinized solutions, and 11 received the control solutions. No statistically significant differences were found between the saline and alkalinized groups with respect to age, height, and weight.

The pH of 1.25% mepivacaine mixed from freshly opened vials was 5.55. The pH of the mepivacaine plus saline was 5.55. The pH of the alkalinized mepivacaine was 7.30.

Figures 1 and 2 show the percentage of patients in both groups in whom analgesia and anesthesia developed, respectively, in each of the terminal nerves of the brachial plexus. There were no statistically significant differences between the alkalinized and saline groups with respect to distribution of nerve blockade.

Figure 3 shows the mean time to onset of analgesia in each of the terminal nerves of the brachial plexus. There were no statistically significant differences between the groups in time to onset of analgesia. Figure 4 shows the mean time to onset of anesthesia in each of the terminal nerves of the brachial plexus. Alkalinization significantly shortened the time to onset of anesthesia in the medial cutaneous nerve of the forearm, the median nerve, and the ulnar nerve.

Figures 5 and 6 show the mean time to onset of proximal and distal paresis and paralysis. There was no significant difference in time to onset of paresis, but alkalinization significantly shortened the time to onset of both proximal and distal paralysis. Alkalinization had no significant effect on the number of patients in whom paresis or paralysis developed.

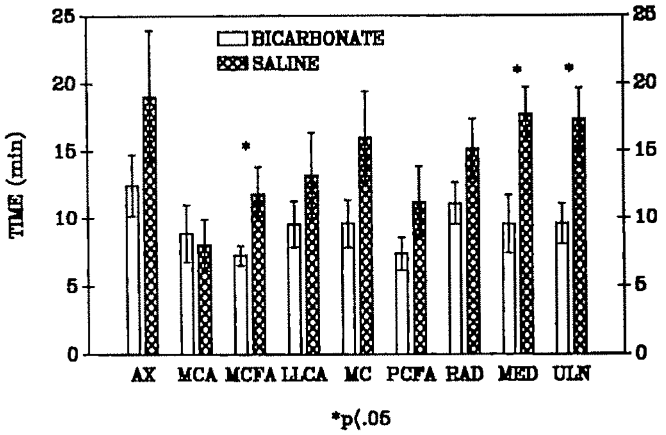

Figure 4. Mean time to onset of anesthesia in minutes is plotted for each of the terminal nerves of the brachial plexus. Error bars depict standard error of the mean. *Asterisks* denote significant differences between the alkalinized and placebo groups.

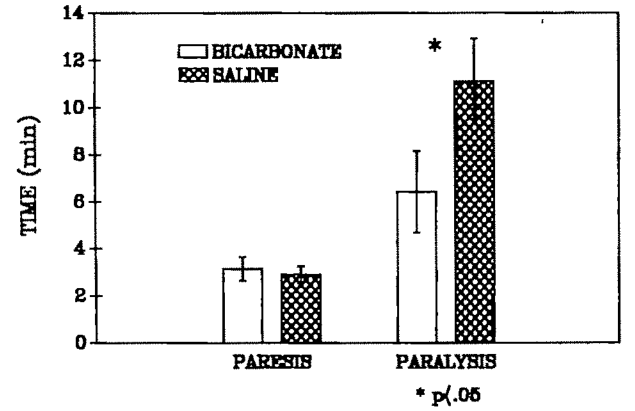

Figure 5. Mean time to onset of paresis and paralysis of forearm extension at the elbow (proximal motor block) is plotted for the placebo and alkalinized groups. Error bars are standard error of the mean. *Asterisks* denote significant differences between the groups.

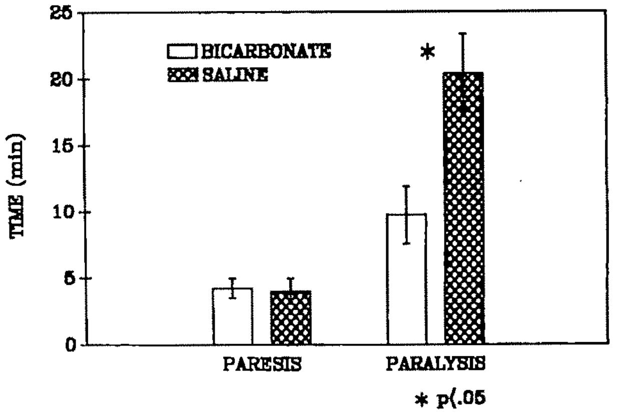

Figure 6. Mean time to onset of paresis and paralysis in the hand (distal motor block) is plotted for the placebo and alkalinized groups. Error bars are standard error of the mean. *Asterisks* denote significant differences between the groups.

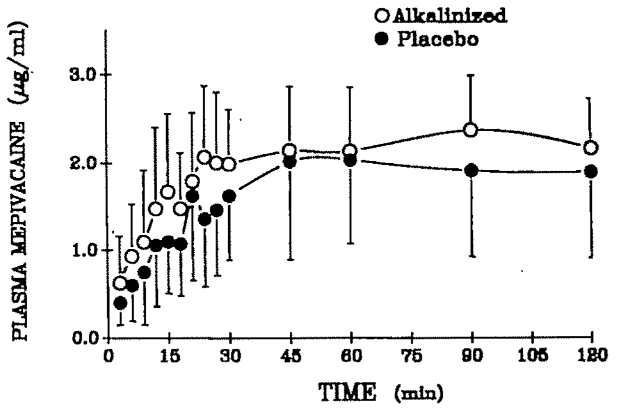

Figure 7. Mean plasma mepivacaine concentration after axillary block (as determined by gas chromatography) is plotted at the specified time points for the alkalinized and placebo groups. Error bars denote the standard error of the mean.

Figure 7 shows the mean venous plasma concentrations of mepivacaine at each of the sampling times for both the alkalinized and saline groups. Although mean mepivacaine concentrations were slightly greater in the alkalinized group, the difference was not statistically significant.

Discussion

Calculations based on the Henderson-Hasselbach equation reveal that alkalinization of mepivacaine from a pH of 5.55 to 7.30 increases the percentage of mepivacaine present as the free base from less than 1% to 33%. It is the un-ionized free-base moiety that can cross connective tissue barriers and the nerve cell membrane to gain access to the site of action of local anesthetics. Alkalinization of local anesthetics speeds onset of blockade of nerve conduction in vitro (10). Studies in epidural blockade have confirmed faster onset of sensory block with alkalinized agents in vivo (1–3).

Previous studies with alkalinized agents in brachial plexus block have yielded conflicting results. Hilgier (4) found that alkalinization of bupivacaine with epinephrine from a pH of 3.9 to 6.4 decreased time to onset of analgesia to pinprick from an average of 24.3 min to 9.8 min in subclavian brachial plexus block. The distribution of the blockade that resulted was not stated. However, alkalinization of bupivacaine without epinephrine from a pH of 5.5 to 7.10 in subclavian brachial plexus block failed to produce a difference in time to onset of sensory blockade as measured by awareness of pinprick (anesthesia), or in time to onset of motor blockade or time to peak motor blockade (5). Alkalinization of mepivacaine from a pH of 5.83 to 7.31 in subclavian block decreased the time to onset of sensory analgesia in the distribution of the musculocutaneous, median, radial, and ulnar nerves to one-third to one-half of that of the plain solution, as well as speeded onset of motor blockade of the proximal portion of the arm (6). However, Berman et al. (7) reported that alkalinization of mepivacaine did not speed onset of axillary block as measured by a sensory and motor scoring system; the pH of the agents compared was not stated.

We found that alkalinization had no significant effect on the development of analgesia but did hasten the onset of anesthesia in several of the terminal nerves. Alkalinization did not affect the frequency of successful blockade of any of the terminal nerves of the brachial plexus.

There are several factors that may account for these contradictory results regarding the ability of alkalinization to speed onset of blockade.

Degree of pH change. Study of alkalinized agents in epidural anesthesia has demonstrated that the degree of improvement in time to onset is directly related to the extent of difference in the pH of the solutions compared (2). A similar pH dependence was noted in a study of carbonated local anesthetics of varying pH (11). One would therefore expect to find a large decrease in time to onset of block with a large increase in pH (4), and less or no shortening of time to onset with a smaller change in pH (5). Although variation in magnitude of pH change is likely a major factor in explaining these inconsistent results, it is unlikely that this is the only operative factor. Our pH change for mepivacaine was comparable to that used by previous authors (6). That study demonstrated a profound decline in time to onset of analgesia, yet we noted a decrease of time to onset for anesthesia but not for analgesia.

Epinephrine effect. Studies that have demonstrated an effect of alkalinization have generally utilized epinephrine, whereas studies with a negative result have not. However, it is unlikely that the presence of epinephrine is necessary for alkalinization to achieve its effect, as epinephrine was not required for decreasing time to onset of blockade in vitro (10), and we noted an effect of alkalinization in the absence of epinephrine.

β-Error. Neither of the studies that asserted a lack of effect with alkalinized anesthetics calculated their probability of a beta (type II) error, which is the probability of concluding that a treatment has no effect when in reality it does.

Increasing the amount of free base of local anesthetic could also augment absorbtion of local anesthetic into the systemic circulation in addition to enhancing neural blockade. As noted previously, it is the un-ionized free-base moiety that is best able to cross connective tissue barriers. Alkalinized anesthetics might therefore result in enhanced absorbtion and an increased frequency of systemic toxicity. We found that alkalinization resulted in a slight increase in venous mepivacaine concentration that did not achieve statistical significance. The time-course, concentrations, and lack of difference with alkalinization are in agreement with previously published data (7).

We conclude that alkalinized mepivacaine offers the advantage of quicker onset of more profound blockade in several terminal nerve distributions. Alkalinization does not result in statistically significantly greater blood concentrations of mepivacaine.

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Analgesic Effect of Capsaicin in Idiopathic Trigeminal Neuralgia

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Twelve informed and consenting patients were studied to determine the influence of capsaicin, the pungent component of the red pepper, on trigeminal neuralgia. All of these patients had idiopathic trigeminal neuralgia. These patients were followed up for 1 yr after the topical application over the painful area of 1.0 g of capsaicin three times a day for several days. Six patients had complete and four patients had partial relief of pain; the remaining two patients had no relief of pain. Of the 10 patients who were responsive to therapy, four had relapses of pain in 95–149 days. There were no relapses following the second therapy for the remainder of the year. We conclude that the topical application of capsaicin is frequently successful in relieving the pain from trigeminal neuralgia.

(Anesth Analg 1992;74:375–7)

Trigeminal neuralgia is characterized by an intense paroxysmal pain, strictly confined to the area innervated by one or more branches of the trigeminal nerve. Capsaicin, the pungent component of the red pepper, selectively stimulates then blocks a subclass of primary sensory neurons with possible nociceptive functions (1–3). Considering this selective action, capsaicin has been proposed for the treatment of localized pain syndromes (4,5). Repeated applications of capsaicin have been shown to reduce pain in patients affected by several pain syndromes (6–10). In the present open-label study, the effect of repeated topical applications of capsaicin was evaluated on patients during an active period of pain attacks due to idiopathic trigeminal neuralgia (ITN). All patients were followed up for 1 yr. During this period, four patients in whom capsaicin therapy was successful but who experienced a relapse of the neuralgia were treated by a further cycle of drug applications.

Methods

Twelve informed and consenting patients (5 men and 7 women; mean age ± SEM, 65.4 ± 3.2 yr) suffering from ITN were included in the study. The approval of the Ethical Committee of our Institute was obtained in advance. The patients were selected from those who were in the active period of neuralgia, with daily attacks over a long period of time. The duration of the illness varied from 2 to 10 yr, and the current episode was unremitting for 2 to 6 mo. Pain was localized along the maxillary branch in four patients and along the mandibular branch in three patients. Four patients showed a combination of the maxillary and mandibular ITN; the remaining patient was affected in the ophthalmic and maxillary branch. All patients had previously undergone therapy with carbamazepine, which in three cases relieved pain but was stopped because of its adverse side effects. Administration of other pharmacologic agents (i.e., phenytoin) was not effective in relieving pain. In each case, previous treatments were suspended at least 10 days before starting capsaicin treatment. None of the patients had undergone surgical procedures for relief of ITN.

The patients were instructed to apply (three times a day for several days) approximately 1 g of a cream containing capsaicin (0.05%) to the cutaneous area corresponding to the affected trigeminal branch. Trigger points, if they existed, were included within the area that received treatment. The patients were warned not to apply cream on the eyelid or on the periocular regions, being told that accidental contact with the conjunctiva or other ocular tissues would produce an intense irritation or worse—permanent damage in these structures. During capsaicin treatment, a follow-up visit was carried out every 3 days to assess (with a patient's self-evaluation) the intensity of the burning sensation evoked by capsaicin and the pain severity of ITN. One of the daily applications of capsaicin was performed during each follow-up

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Table 1. Simultaneous Reduction of Both Capsaicin-Induced Burning Sensation and Severity of the Trigeminal Neuralgia During Capsaicin Treatment[a]

Patient No.	Baseline values		Days of follow-up													
			3rd		6th		9th		12th		15th		18th		21st	
	BS	PS	BS	PS	BS	PS	BS	PS	BS	PS	BS	PS	BS	PS	BS	PS
1	4	9	3	8	3	8	2	6	1	4	1	3	1	3	1	3
2	4	8	3	8	3	6	3	5	2	2	1	0	1	0	1	0
3	4	10	4	9	2	7	2	3	1	0	1	0	0	0	0	0
4	4	8	4	6	3	6	2	4	2	0	1	0	1	0	1	0
5	4	9	3	9	3	7	2	8	1	9	1	8	1	8	0	8
6	4	7	3	8	3	7	1	4	1	4	1	3	1	0	1	0
7	4	9	4	8	3	6	2	2	2	3	1	4	0	4	1	4
8	4	8	3	8	3	7	2	4	1	1	2	0	1	0	0	0
9	4	8	4	9	3	7	2	9	2	9	1	8	1	8	0	8
10	4	9	4	9	2	6	1	6	1	4	0	2	0	2	0	2
11	4	10	3	9	3	7	2	5	1	3	1	3	1	1	1	0
12	4	9	4	8	3	5	2	6	1	2	1	2	1	2	0	2

BS, burning sensation; PS, pain severity.

[a] Burning sensation was scored using a numeric rating scale of 0 to 4. Pain severity was scored using a numeric verbal scale of 0 to 10.

visit, and the burning sensation evoked at that time was used as a parameter for evaluation. The intensity of the burning sensation was scored using a numeric rating scale (0–4), assigning as a maximum value the burning sensation experienced at the first application. A decrease in burning sensation was considered as an index of desensitization to the drug; then when it was no longer experienced, treatment was terminated. Pain severity was rated on a scale of 0–10 (0 = no pain, 2 = very mild, 4 = mild, 6 = moderate, 8 = severe, 10 = very severe), which was based on an average of the frequency, duration, and intensity of the pain attacks experienced during the days between each follow-up session. A baseline measurement of the pain severity was done before beginning the treatments. A careful neurologic examination, which included sensory testing of the treated area, was carried out before and after the cycle of applications. After capsaicin treatment, all patients were seen at least on a monthly basis for 1 yr.

The data have been analyzed by the following nonparametric statistical methods (11): Friedman's test (for the variance of the burning sensation as well as pain severity); Wilcoxon's signed rank test (for comparison of the pain severity score assessed during each session of observation with the score of the previous session's observation); Kendall's coefficient (for the correlation of the decrease of burning sensation and pain severity during treatment) (11).

Results

Neurologic examination did not show alteration in the sensory function of the treated area either before or after capsaicin applications, except for two patients who showed a transitory hyperesthesia during the first 5 days after capsaicin treatment. Topical capsaicin was applied until the acute burning sensation produced by the drug was no longer present (Table 1). The application of capsaicin on the trigger point, where existing, did not evoke any different response.

A significant variance of burning sensation and pain severity was found by comparing the values observed during the treatment with those of pretreatment measurement ($P < 0.01$, Friedman's test). The reduction in the severity of the pathological pain had a statistical significance between the scores from the 3rd to the 15th days of follow-up (6th vs 3rd and 9th vs 6th: $P < 0.05$; 12th vs 9th and 15th vs 12th: $P < 0.01$; Wilcoxon's signed rank test). The reduction of the pain severity was statistically related to the decrease in burning sensation (Kendall's coefficient of relation = 36.7, $P < 0.01$) (Table 1).

Considering the single cases, six patients showed a decrease in, leading to the complete disappearance of, the pain attacks; four of them reported an improvement from 60% to 80% in comparison with the initial condition. The remaining two patients showed no effect.

During the year following the initial capsaicin treatment, six of the 10 patients sensitive to the therapy did not suffer from neuralgia again. The remaining four patients experienced a relapse of ITN after a variable period of time. In three of these patients, a second cycle of capsaicin applications was again fully effective in relieving pain. The second treatment followed the same procedure as the first one. The burning sensation evoked by the first appli-

Table 2. Effect of a Second Cycle of Capsaicin Applications in Patients With a Relapse of the Trigeminal Neuralgia[a]

Patient No.	Sex	Age (yr)	PSFT	TWP (days)	PSNE	DST (days)	PSST
1	M	68	0	135	8	16	0
2	M	63	0	149	10	15	8
3	F	71	2	95	10	15	2
4	M	66	3	110	10	18	0

DST, duration of the second treatment (determined on the observations of the decrease and disappearance of the burning sensation evoked by capsaicin); PSFT, pain severity immediately at the end of the first treatment; PSNE, pain severity of the new episode detected at the beginning of the new cycle of applications; PSST, pain severity immediately at the end of the second treatment; TWP, time without pain after which a relapse occurred.

[a] Pain severity was measured by means of a numeric verbal scale (0–10).

cation of the second cycle of treatment was similar to that evoked by the first application of the previous cycle. After the second treatment, in the patients sensitive to the therapy, there was no ITN relapse until the end of the follow-up year (Table 2).

Discussion

Repeated topical applications of capsaicin on the cutaneous area corresponding to the trigeminal branches affected by ITN seem to be effective in relieving pain episodes. The possibility of a placebo effect cannot be excluded by the open-label procedure of the present pilot study. At present, a controlled procedure seems unfeasible because of the difficulty of finding a placebo capable of mimicking the acute local effects of capsaicin (burning sensation, reddening) as well as their progressive decrease during the following applications of the drug. Nevertheless, in most of the cases where neuralgia reoccurred, the repetition of the therapy again relieved the pain attacks. The evidence that the beneficial effect of capsaicin is repeatable supports the view that it could not be due to a spontaneous remission of the illness, or to some other nonspecific mechanisms, but is due precisely to a selective action of capsaicin.

Assuming that capsaicin exerts a specific therapeutic effect on ITN, it is not clear if this effect is due to a counterirritation or to a reversible selective impairment of the cutaneous trigeminal afferents. However, present findings show that the progressive decrease in symptomatology has a similar time-course to the reduction of the acute burning effect produced locally by capsaicin. This suggests that the amelioration might be dependent upon a transitory impairment of certain trigeminal sensory neurons. In particular, the repeated exposures to capsaicin could deplete (or inhibit the transport toward central structures) the neuropeptides, such as substance P, neurokinin A, and calcitonin gene-related peptide, which are contained in the sensory neurons sensitive to capsaicin.

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ORIGINAL ARTICLES

Differential Relaxant Effect of High Concentrations of Intravenous Anesthetics on Endothelin-Constricted Proximal and Distal Canine Coronary Arteries

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This study determined the direct effect of three intravenous anesthetics on isolated canine coronary arteries constricted with the potent endogenous vasoconstrictor endothelin. Arteries were divided into groups of large (1.3–2.5 mm) and small (250–500 μm) vessels, and arterial rings were suspended in tissue baths. The rings were stretched to an optimal resting tension and then preconstricted with an EC_{50} concentration of endothelin that was equivalent for both groups. Incremental concentrations (5×10^{-6} M to 1.6×10^{-2} M) of thiopental, ketamine, and propofol were added to the baths, and the relaxant responses were recorded. Small arteries demonstrated greater vasodilation at equivalent drug concentrations than did large arteries. These results demonstrate antagonism of the vasoconstrictor endothelin by intravenous anesthetics. Distal vessels are more sensitive than proximal vessels to the relaxant effects of the intravenous anesthetics studied. Direct effects on coronary vascular tone, however, are only apparent at concentrations above those seen clinically. Despite the potential for a differential effect on proximal and distal coronary arteries, we conclude that thiopental, ketamine, and propofol do not possess a direct effect on the tone of large or small canine coronary arteries at concentrations seen in routine clinical practice.

(Anesth Analg 1992;74:378–83)

Hypotension commonly follows induction of anesthesia with many though not all intravenously administered anesthetics. In healthy subjects and in patients with ischemic heart disease, intravenous anesthetics cause a decrease in arterial blood pressure with relative preservation of cardiac output (1,2). Several studies have demonstrated that intravenous anesthetics induce relaxation in various preconstricted vessels including coronary arteries (3,4), and different vascular beds vary in their capacity to dilate in response to these anesthetics (3,5). The relative effect of intravenous anesthetics on epicardial conduit and resistance vessels, however, remains unknown.

Endothelin is a potent and efficacious vasoconstrictor produced by vascular endothelial cells (6). Concentrations of this substance are increased in human plasma during surgery (7). Furthermore, the interaction of endothelin and endothelium-derived relaxing factor with a newly described product of vascular smooth muscle in coronary autoregulation has recently been suggested (8,9).

The morphology and function of proximal and distal coronary arteries differ. Studies in animals and in humans suggest that there are differences in the responses to vasoactive agents between proximal and distal coronary arteries (10,11). The influence of endothelin on large and small coronary arteries is also unknown. Although intravenous anesthetics relax cerebral vessels preconstricted with endothelin (12), the effect of these agents on coronary vessels exposed to endothelin has not been investigated.

As intravenous anesthetics may alter systemic hemodynamics and may have direct effects on the coronary circulation, the effects of anesthetics in vivo represent a combination of multiple actions. In this study, isolated coronary arterial segments were used to avoid the confounding effects of intravenous anesthetics on systemic hemodynamics; thus, the direct effects of these agents on coronary arteries were investigated. Thiopental and ketamine are two widely used intravenous anesthetics differing substantially in their apparent effects on vascular tone. Propofol, a relatively new intravenous anesthetic,

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causes a significant decrease in blood pressure. The vasorelaxant effects of these three anesthetics were determined in large and small canine coronary arteries preconstricted with endothelin.

Methods

All experimental procedures and protocols used in this investigation were approved by the Animal Care Committee of the Medical College of Wisconsin, conformed to the Guiding Principles in the Care and Use of Animals of the American Physiological Society, and were in accordance with the Guide for Care and Use of Laboratory Animals. Twenty-three adult mongrel dogs of either sex were killed after they were intravenously anesthetized with 25 mg/kg of pentobarbital sodium, and the hearts were removed. Segments of the proximal left anterior descending coronary artery (large) and first- and second-order branches of the left anterior descending coronary artery (small) were identified, immediately dissected free, and placed in physiological saline solution of the following millimolar composition: NaCl 119, KCl 4.7, $MgSO_4$ 1.17, $CaCl_2$ 1.6, $NaHCO_3$ 27.8, NaH_2PO_4 1.18, ethylenediaminetetraacetic acid 0.026, glucose 5.5, and HEPES (4-[2-hydroxyethyl]-1-piperazine ethanesulfonic acid). Using a dissecting microscope, the vessels were cleaned of surrounding fat and connective and other nonvascular tissue, with special care being taken to avoid injury to the luminal surface. The vessels were divided into rings 0.4–0.5 cm long. The rings were mounted on tungsten triangles, the lowermost of which was fixed whereas the other was attached to a force displacement transducer (Grass Force-Displacement Transducer FT03, Grass Instrument Company, Quincy, Mass.), and suspended in jacketed temperature-controlled (37°C) tissue baths containing physiological saline solution aerated with 93.5% O_2 and 6.5% CO_2. Half-hourly measurements were made of Pco_2 and Po_2, and these gas tensions were kept constant at a pH of 7.38–7.42, a Pco_2 of 35 mm Hg, and a Po_2 greater than 450 mm Hg.

Vascular rings were divided into two groups consisting of small (diameter 250–500 μm) and large (diameter 1300–2500 μm) vessels. Optimal resting tension was determined in preliminary studies by gradually stretching rings and determining the response to KCl (40 mM) at each level of tension. Each ring was gradually stretched to the predetermined optimal resting tension and was allowed to equilibrate for at least 2 h. Tension was continuously recorded on a polygraph (Grass, model 7 polygraph). The functional integrity of each ring was then assessed by measuring the contractile response evoked by increasing the bath K^+ concentration to 40 mM. KCl exposure was followed by a washout, and the process was repeated at 30-min intervals until a stable (i.e., a response differing by less than 15% from the previous) response was obtained. A minimum of two to three successive exposures to KCl was necessary to ensure a stable response. The functional integrity of the vascular endothelium was assessed by the response to the endothelium-dependent vasodilator acetylcholine. Each vessel was constricted with KCl, and the response to a single exposure of acetylcholine (10^{-5} M) was determined. A relaxant response of less than 40% of the KCl-induced contraction was regarded as unsatisfactory, and the ring was discarded. In 30 rings (five dogs), endothelin was added to the tissue baths in six increasing concentrations from 10^{-10} M to 10^{-6} M, at which point a plateau effect was evident in the contractile response of both large and small vessels. The concentration required for 50% maximal contraction (EC_{50}) for large and small coronary arteries was then calculated.

In separate experiments, large and small vessels were partially preconstricted with an EC_{50} concentration of endothelin and were exposed to incrementally increasing and equimolar concentrations of either thiopental, ketamine, or propofol (range, 5×10^{-6} M to 1.6×10^{-2} M). Each vessel was exposed to only one randomly determined anesthetic. Eight coronary segments (four proximal, four distal) were studied simultaneously. Measurements were made of relaxant responses after 1–2-min exposure to a given anesthetic concentration. At the end of each experiment, 10^{-4} M papaverine was added to determine maximal relaxation.

The following drugs were used: acetylcholine, papaverine, endothelin 1 (Sigma Chemical Co., St. Louis, Mo.); thiopental sodium (Abbott Laboratories, North Chicago, Ill.); ketamine chloride (Parke Davis, Morris Plains, N.J.); propofol (Stuart Pharmaceuticals, Wilmington, Del.). Intralipid 10% (KabiVitrum, U.K.) was used as the propofol vehicle. The endothelin was obtained in the lyophilized form, reconstituted, and divided into smaller aliquots before being relyophilized and stored at −20°C. Fresh solutions of each drug were prepared on the day of each experiment.

Data are expressed as mean ± SEM. Relaxation produced by the anesthetic agents was expressed as a percentage of that produced by papaverine. Relaxant responses to the anesthetics were compared using a two-way analysis of variance for repeated measures, followed by the application of Duncan's *t*-test if the F value was significant. A value of $P < 0.05$ was considered significant.

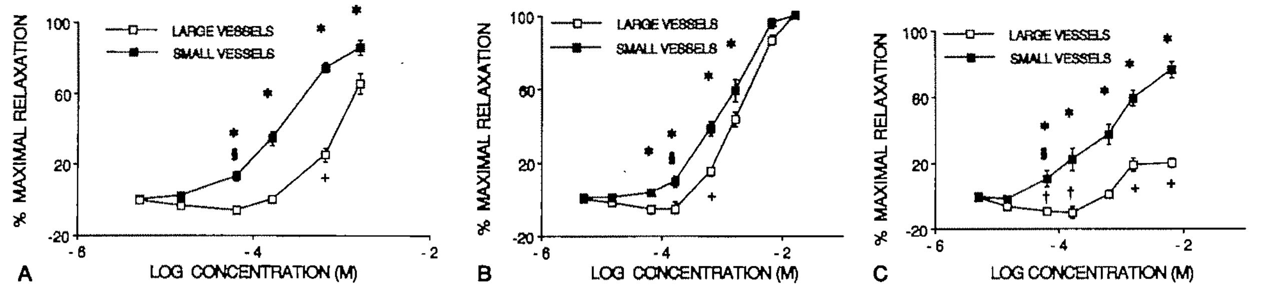

Figure 1. Effect of increasing concentrations of (A) thiopental (14 large vessels, 7 dogs; 14 small vessels, 8 dogs), (B) ketamine (12 large vessels, 7 dogs; 11 small vessels, 6 dogs), and (C) propofol (12 large vessels, 7 dogs; 13 small vessels, 7 dogs) on tone of proximal and distal coronary vessels contracted with an EC_{50} concentration of endothelin. Mean ± SEM data. *Significant ($P < 0.05$) difference between proximal and distal vessels. †Significant ($P < 0.05$) increase in tension of proximal vessels. +Significant ($P < 0.05$) decrease in tension of proximal vessels. §Significant ($P < 0.05$) decrease in tension of distal vessels.

Results

Only vessels demonstrating a consistent contractile response to 40 mM KCl and a satisfactory relaxation (of at least 40% of the preconstricted value) to 10^{-5} M acetylcholine were included in the study. A total of 119 rings harvested from 23 dogs were used. Because of inadequate endothelial responses, 23 rings were discarded. Mean vessel diameters were 2100 ± 31 and 428 ± 34 μm for large and small arteries, respectively. Optimal resting tensions were 1500 and 750 mg for large and small arteries, respectively.

Response to Endothelin

The potency of endothelin in the two-vessel groups did not differ significantly. The EC_{50} for large (10 vessels, 3 dogs) and small vessels (10 vessels, 3 dogs) was $3.05 \pm 0.32 \times 10^{-8}$ and $3.35 \pm 0.35 \times 10^{-8}$ M, respectively ($P > 0.05$).

Response to Thiopental

Thiopental significantly ($P < 0.05$) relaxed coronary vessels preconstricted with endothelin to 65% ± 5.7% of the maximal response in large arteries (14 vessels, 7 dogs) and 86% ± 4.3% in small arteries (14 vessels, 8 dogs; Figure 1A). Concentrations of thiopental higher than 1.7×10^{-3} M caused the pH in tissue baths to increase, but concentrations higher than this were not investigated. Small vessels dilated to a significantly greater degree than did large vessels (Figures 1A and 2). The increase in tension observed at low concentrations of thiopental was not significant.

Response to Ketamine

Ketamine totally relaxed large (12 vessels, 7 dogs) and small (11 vessels, 6 dogs) coronary vessels preconstricted with endothelin at a concentration of 1.6×10^{-2} M. At concentrations lower than this, small vessels dilated to a significantly greater degree than did large vessels (Figure 1B). Vasoconstriction observed at low concentrations of ketamine was not significant.

Response to Propofol

Propofol relaxed vessels preconstricted with endothelin to 19% ± 6.3% of the maximal response in large vessels (12 vessels, 7 dogs) and 76% ± 5.1% in small vessels (13 vessels, 7 dogs, Figure 1C). Small vessels relaxed to a significantly greater degree than large vessels. Large vessels demonstrated significant though slight vasoconstriction at lower concentrations of propofol. This response changed to dilation when the concentration of propofol was further increased. No response in either group of vessels was elicited by the propofol vehicle.

In large vessels (Figure 3), significant differences in responses were evident between the three anesthetics. At the largest concentrations, thiopental had the most relaxant effect, propofol the least, and ketamine was intermediate in effect.

Discussion

Results of the present investigation confirm the vasoconstrictor effect of endothelin on the isolated coronary vessel. The intravenous anesthetics—thiopental, ketamine, and propofol—relax both large and small coronary arteries preconstricted with endothelin although only at concentrations higher than those observed clinically. Small coronary vessels dilated more than large vessels in response to all anesthetics. Propofol, a recently introduced intravenous anesthetic, enhanced endothelin-induced vasoconstriction at low concentrations in large arteries.

In this investigation, an isolated vascular ring preparation was used, which offered the advantages

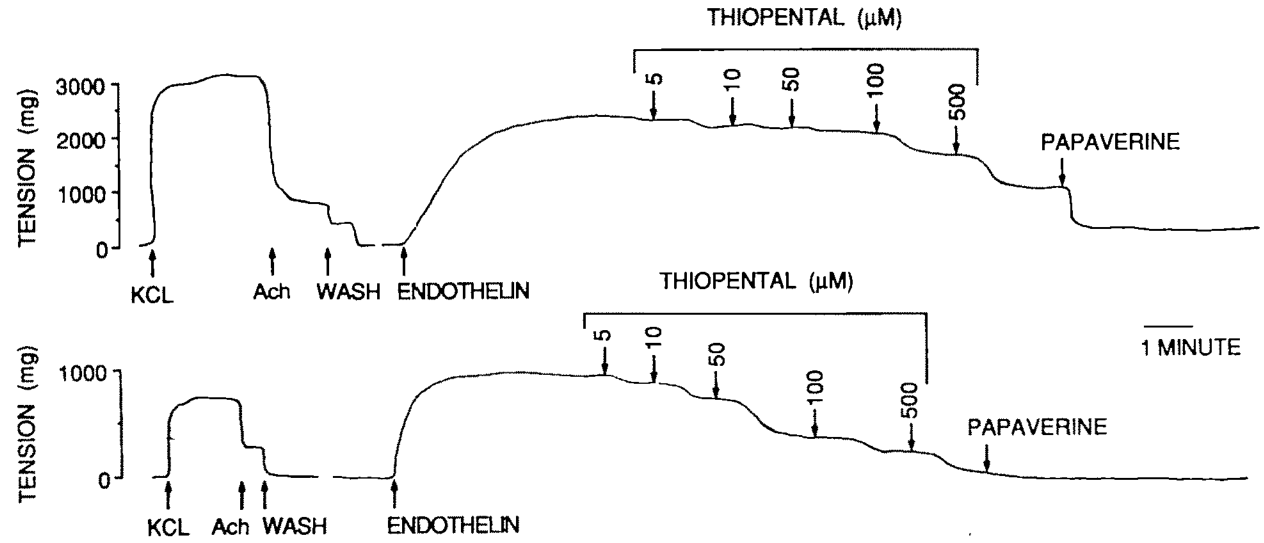

Figure 2. Isometric tension recordings of the responses to thiopental of proximal (*top*) and distal (*bottom*) coronary arteries preconstricted with endothelin. Thiopental attenuated the endothelin-induced contraction at high concentrations. The vasorelaxant effect is more pronounced in the distal artery.

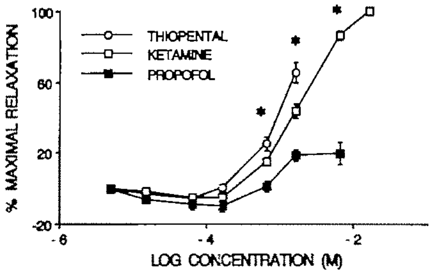

Figure 3. Effect of thiopental (14 vessels, 7 dogs), ketamine (12 vessels, 7 dogs), and propofol (12 vessels, 7 dogs) on canine proximal coronary vessels constricted with endothelin. Mean ± SEM data. *Significant ($P < 0.05$) differences between all groups at a given concentration.

of quantifying direct effects of drugs on vascular tone and of eliminating changes secondary to alterations in systemic hemodynamics, myocardial function, and the central nervous system. As regulation of coronary vascular tone has been shown to be differentially modulated in large and small arteries (10,11,13), both vessel sizes were selected for this study. Incubation of the arterial tissue for several hours in a frequently exchanged physiologic salt solution before the collection of data minimized the possible effects of residual pentobarbital.

Endothelin is a 21 aminopeptide released by endothelial cells (6). It is released in response to multiple stimuli including catecholamines, coagulation factors, cytokines, and surgical trauma (6,7). Recently, a role of this substance in the regulation of local blood flow has been suggested (6): In the normal state, the relative balance of endothelin and endothelium-derived relaxing factor in a vascular segment may modulate flow. The actions of endothelin may be opposed by endothelium-derived relaxing factor and by a recently described product of vascular smooth muscle that inhibits endothelin release (9,14). In disease states, the effects of endothelin may predominate (14). Measurement of endothelin activity in disease states has implied a role in the pathogenesis of a variety of conditions such as unstable angina (15), myocardial infarction (16), and subarachnoid hemorrhage (17). Furthermore, aortic cross-clamping is associated with release of this peptide, and subvasoconstrictor concentrations of endothelin potentiate the contractions to norepinephrine and serotonin in human arteries (18,19). The present results confirm those of Larkin et al. (20) who found that endothelin produced intense ischemia by direct vasoconstriction of coronary arteries in dogs, although the concentrations of endothelin used in the present study far exceed those reported in vivo (7,17).

Thiobarbiturates constrict vascular smooth muscle (3). For example, Hatano et al. (5) demonstrated a vasoconstrictor response in mechanically stretched coronary vessels exposed to thiobarbiturates. The induction of a submaximal degree of vascular contraction, as in the present study, may resemble more closely the in vivo situation. The present results substantiate Van Nueten's (21) suggestion that preconstriction may be necessary to unmask a potential vasodilator effect. In partially constricted cerebral and mesenteric vessels, a biphasic response to thiobarbiturates occurs, with contraction evident at low concentrations and relaxation developing as concentrations increase (22). Although there was a slight constriction in the large coronary artery, this was not statistically significant. However, thiopental is not the most potent of the thiobarbiturates with respect to vasoconstriction (5). In contrast to large vessels, constriction did not occur in small coronary arteries exposed to thiopental.

Ketamine has potent cardiovascular effects with changes in autonomic tone, blood pressure, and cardiac output. These are thought to be predominantly reflex in origin (23). In the present investigation, ketamine relaxed large and small coronary arteries. This was consistent with the findings of Stowe et al. (24) who demonstrated increased coronary flow with a decrease in oxygen extraction in the isolated perfused heart exposed to ketamine at concentrations lower than those found to relax coronary vessels in the present study.

Propofol, a recently introduced intravenous anesthetic, has been described to possess significant vasodilator properties that produced a decrease in arterial blood pressure during induction of anesthesia (25). There are few studies concerning the direct effects of propofol in isolated vessels. Dose-related vasodilation has been demonstrated to occur in potassium-constricted hepatic artery and portal vein (4). In a study of quiescent porcine coronary vessels exposed to 10^{-4} M propofol, slight relaxation was observed (26). In the present study, in which vessels were partially preconstricted, a modest vasoconstrictor effect of propofol occurred at low concentrations whereas dilation occurred at higher concentrations.

The relative resistance demonstrated by larger coronary vessels to the vasodilator effects of all three agents examined corresponds with a conductive function for these vessels. Smaller vessels determine resistance and flow in the coronary circulation. In an isolated heart preparation, intravenous anesthetics increase total coronary flow (24,27). This is consistent with the findings of the present investigation that demonstrate a significantly greater vasodilator effect in distal vessels. In a whole-animal model, pentobarbital causes redistribution of coronary blood flow from subendocardium to subepicardium; however, this may be due to associated tachycardia and to increased catecholamine concentrations (28). There is a considerable number of functional differences between large and small coronary vessels including a differential distribution of adrenergic receptors (10). Furthermore, vasoactive peptides such as vasopressin and serotonin exert differing or contrasting effects on vessels of different sizes (29). Serotonin, a known specific dilator of distal coronary arteries has little effect on vessels of the size used in this study (29). Smaller arteries may be influenced by metabolic factors such as adenosine, which has a more potent effect in relaxing these vessels (13). The present results indicate that intravenous anesthetics can be included among the substances that may exert a relatively specific effect on distal coronary vessels.

In this study, all three anesthetics attenuated the endothelin-induced vasoconstriction in both vessel groups at higher concentrations. Clinically observed concentrations of thiopental (1–3 × 10^{-4} M) (30), ketamine (1–6 × 10^{-5} M) (31), and propofol (1–3 × 10^{-5} M) (25) do not affect the tone in the epicardial coronary vessels used in this study. Direct effects on vessels distal to these remain to be investigated. Despite the potential for a differential effect on proximal and distal coronary arteries, however, we conclude that the intravenous anesthetics (thiopental, ketamine, and propofol), do not possess a direct effect on the tone of large or small canine coronary arteries at concentrations seen in routine clinical practice.

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Halothane Reduces Dysrhythmias and Improves Contractile Function After Global Hypoperfusion in Isolated Hearts

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We investigated the effects of halothane on changes in cardiac function during hypoperfusion and recovery of function after reperfusion in the isolated perfused guinea pig heart. Heart rate, atrioventricular (AV) conduction time, the incidence and severity of dysrhythmias, and isovolumetric left ventricular systolic pressure (LVSP) and its derivative were measured. Hearts (n = 85) were divided into three groups for 30 min of perfusion at 0% (no flow), 10%, and 25% of the control perfusion pressure (PP, 55 mm Hg). These groups were subdivided and exposed to 0%, 0.74% (0.23 ± 0.01 mM), or 1.65% (0.51 ± 0.01 mM) halothane 10 min before, during, and 10 min after hypoperfusion. Hypoperfusion was followed by 40 min of reperfusion at control PP. Exposure to 0.74% and 1.65% halothane before hypoperfusion produced a 9% and 13% decrease in heart rate, a 2% and 30% increase in AV conduction time, and a 25% and 51% decrease in LVSP and $dLVP/dt_{max}$, respectively. During the 30 min of hypoperfusion, heart rate decreased and AV conduction time increased; second- and third-degree AV block occurred in all hearts in the 0% and 10% PP groups, but only in some hearts in the 25% PP groups. Left ventricular systolic pressure rapidly decreased during hypoperfusion in all groups. During early reperfusion ventricular fibrillation and ventricular tachycardia occurred in the 0% and 10% PP groups but not in the 25% PP groups. During reperfusion 0.74% and 1.65% halothane greatly reduced the duration of ventricular fibrillation from 8.1 ± 3.3 min to 1.5 ± 0.8 and 1.9 ± 1.2 min in the 0% and 10% PP groups, respectively. A concentration of 0.74% halothane increased the incidence of supraventricular tachycardia on reperfusion in the 10% group (from a control of 20% to 65%), and 1.65% halothane increased the duration (2.6 ± 2.5 min) and incidence (38%) of supraventricular tachycardia on reperfusion in the 0% PP group. A concentration of 1.65% halothane facilitated recovery of LVSP after hypoperfusion in the 25% group but not in the 0% and 10% PP groups. These results indicate that halothane, in some instances, can have protective cardiac effects after graded hypoperfusion as assessed by improved contractility and by reduced severity of some dysrhythmias during reperfusion; however halothane may also increase the incidence of supraventricular tachycardia. The cardiac protection by halothane could be a result of reduced cardiac work before, during, and after hypoperfusion, or of some other direct protective cellular effects.

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Coronary hypoperfusion and ischemia can occur during the course of general anesthesia. Reperfusion after ischemia is associated with compromised cardiac function and a variety of dysrhythmias. Although the mechanisms underlying myocardial injury under these conditions are multifactorial and not well understood, excess calcium ion influx and its intracellular accumulation appear to be important events leading to a decline of contractile function and the development of dysrhythmias. Intracellular calcium may increase because of an increase in sarcolemmal permeability to calcium (1), enhanced release of calcium stored intracellularly, decreased capacity of sarcoplasmic reticulum for calcium binding (2), and impaired sodium/calcium exchange (3). Phenomena associated with reperfusion injury of the previously ischemic myocardium are the calcium paradox (4) and the oxygen paradox (5). It has been suggested that free radicals and calcium are simultaneously acting and provoking reperfusion dysrhythmias. In the calcium paradox, mitochondrial damage results from calcium overload, whereas in

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the oxygen paradox, mitochondrial damage is probably initially mediated by free radicals and then followed by calcium overload (6,7). Rapid reperfusion increases the rate of development of reperfusion dysrhythmias (8) and also decreases the recovery of mechanical function (9).

Volatile anesthetics, like calcium entry blockers and β-adrenergic blockers, depress myocardial function, but are not known to block specific receptors altering automaticity, conduction, or contractility of the heart. Calcium entry blockers and β-blockers have potential to protect against ischemia and reperfusion-induced cell injury (10). Because of its potent negative inotropic effects, the volatile anesthetic halothane has been used to limit myocardial oxygen demand and thereby to reduce the occurrence of ischemic episodes in patients undergoing myocardial revascularization (11). Halothane has been shown to decrease both slow (Ca^{2+}) (12,13) and fast (Na^+) ionic channel fluxes (14) as well as to reduce the transient rise of myoplasmic calcium during contraction (15). In addition, under abnormal conditions, halothane depresses calcium accumulation after ischemia or calcium paradox (16,17). Halothane has also been shown to decrease the incidence of dysrhythmias after ischemia and reperfusion in the dog (18) and rat (19), to reduce dysrhythmias after hypoxia in the guinea pig (20), to improve recovery of contractile function of "stunned" myocardium (21), and to reduce myocardial infarct size in the dog (22).

Although a significant volume of knowledge has accumulated regarding protective effects of halothane during ischemia and reperfusion, little is known about the dependency of these effects on the anesthetic concentration or on the degree of global coronary flow reduction. This study was designed to investigate dose dependency and perfusion pressure dependency of changes in cardiac rhythm and contractile function caused by global cardiac hypoperfusion and reperfusion with and without administration of halothane. To investigate only direct cardiac effects, an isolated heart preparation was used.

Methods

The isolated Langendorff heart preparation was selected for study so that extrinsic mechanical, humoral, and autonomic nervous system influences could be avoided. With Institutional Animal Care Committee approval, 85 albino English short-haired guinea pigs (350–450 g) were injected intraperitoneally with 10 mg of ketamine and 1000 U of heparin and were decapitated when unresponsive to noxious stimulation. After thoracotomy, the inferior and superior vena cavae were cut and the aorta was cannulated distal to the aortic valve. The heart was immediately perfused in a retrograde manner through the aorta and was excised. The perfusate, a modified Krebs-Ringer solution, had the following composition (in mM): Na^+, 137; K^+, 4.5; Mg^{2+}, 1.2; Ca^{2+}, 2.5; Cl^-, 134; HCO_3^-, 15.5; $H_2PO_4^-$, 1.2; glucose, 11.5; pyruvate, 2; mannitol, 16; ethylene-diaminetetraacetic acid, 0.05; and insulin, 5 U/L. The solution was equilibrated with a 97% O_2–3% CO_2 gas mixture at a flow rate of 3 L/min. At oxygen tensions above 400 mm Hg, myocardial high-energy phosphate levels are well maintained in isolated hearts perfused with crystalloid solution (23). Global hypoperfusion was induced by switching to different levels of perfusion pressure (PP): 0%, 10%, or 25% of control perfusion pressure (55 mm Hg). Perfusion pressure was maintained at 55 mm Hg during control periods by a 75-cm-high fluid column with an overflow pump (Masterflex 7520, Cole-Palmer, Chicago, Ill.), and was measured at the aortic root with a pressure transducer.

Solution pH, Pco_2, and Po_2 were determined with a blood-gas analyzer (Radiometer ABL-2, Medtron, Des Plaines, Chicago, Ill.). Each heart was perfused with filtered (5 μm) nonrecirculating solution and was submerged in a bath of perfusate solution. The perfusate and bath temperature were maintained at 36.4 ± 0.1°C using a thermostatically controlled water circulating system. Coronary flow was measured with an electromagnetic flowmeter (model BL610-2A, Biotronex Laboratories, Kensington, Md.). Systolic left ventricular pressure (LVSP) was measured isovolumetrically with a transducer connected to a thin, saline-filled latex balloon inserted into the left ventricle through the mitral valve from a cut in the left atrium. Positive and negative $dLVP/dt_{max}$ were measured from the derivative of LVSP obtained electronically. Two pairs of bipolar electrodes (Teflon-coated silver, diameter 125 μm, Cooner Wire Company, Chatsworth, Calif.) were placed in each heart to monitor intracardiac electrograms from which spontaneous heart rate (HR) and atrioventricular conduction time (AVCT) were measured as reported previously (24). The two electrode signals were amplified 100–1000-fold, filtered at frequencies below 100 Hz and above 5 kHz, and displayed continuously on a polygraph (model MT 9500R, Astro-Med, West Warwick, R.I.) and on an image storing oscilloscope (model 5A26, 5113, Tektronix, Beaverton, Ore.). Sinus cycle length was measured and HR was calculated from the right atrial beat-to-beat interval; AVCT was determined from the superior right atrial signal to the right ventricular pulmonary conus signal. Atrial and ventricular electrograms were audibly amplified. Electrograms, LVSP and PP were recorded on tape intermittently (Vetter D1, Vetter Co., Rebersburg, Pa.) for later playback. Electrogram intervals were measured automatically on-line by digital timer systems that allowed instantaneous beat-to-beat interval and rate analyses. Atrioventricular dissociation (AV block) was defined by asynchrony in atrial and ventricular electrogram activity. Atrioventricular block was defined as AV dissociation with a ventricular rate slower than the atrial rate. Ventricular tachycardia was defined by the presence of uniform or multiform ventricular waveforms with AV block and a faster ventricular than atrial rate. Ventricular fibrillation was defined by the presence of erratic activity in the ventricular electrogram and by the absence of pressure generation by the left ventricle. Supraventricular tachycardia was defined by the presence of one-to-one AV conduction, uniform atrial waveforms, and an atrial rate faster than 300 beats/min.

Halothane was administered by switching to perfusate equilibrated with halothane via a vaporizer (Ohio Medical Products, Madison, Wis.) set to deliver 0.75% and 1.5% halothane. Delivered halothane fractions were periodically checked for accuracy by mass spectrometry (Medical Gas Analyzer 1100A, Perkin-Elmer, Norwalk, Conn.). Perfusate (1 mL) was collected at an aortic inflow port into sealed, 2-mL vials before and after hypoperfusion for a head-space analysis of anesthetic concentrations by gas chromatography as described previously (20). Mean halothane concentrations, which were 0.23 ± 0.01 and 0.51 ± 0.01 mM, were calculated to correspond to 0.74% and 1.65% halothane, respectively. This is based on the equivalancy of a partial pressure of 1 vol% halothane to a concentration of 0.31 mM in Krebs-Ringer solution at 37°C at a pressure of 1 atm. There were no differences between halothane concentrations measured before, during, and after hypoperfusion.

Initial control measurements were recorded after a 30-min period of stabilization. All 85 hearts had an LVSP higher than 70 mm Hg during the initial control period and no more than two single premature atrial or ventricular beats per minute. Each heart was exposed to only one level of perfusion and to one halothane concentration or its control. There were a total of nine groups: three groups at each level of hypoperfusion (0% [no perfusion—global ischemia], 10% [90% pressure reduction to 5.5 mm Hg], and 25% [75% pressure reduction to 14 mm Hg]), and within each of these three groups, three subgroups (control [0%], 0.74%, and 1.65% halothane). After a 10-min exposure to 0% (*n* = 29), 0.74% (*n* = 24), or 1.65% halothane (*n* = 24), each heart was perfused for 30 min either at 0%, 10%, or 25% of control PP (55 mm Hg) and then again reperfused for 40 min at the control PP. Therefore, each group consisted of 8–10 hearts. For the halothane groups, halothane was delivered 10 min before hypoperfusion, during hypoperfusion, and for the first 10 min of reperfusion. During 0% perfusion no halothane was delivered to the heart.

Lidocaine (0.5 mL of a 0.1% solution) was injected into the aortic cannula in all hearts 30 min after reperfusion to assess conversion of existing ventricular dysrhythmias and recovery of LVSP. Experiments were terminated 10 min after administration of lidocaine. Measurements were made during the last minute of the initial stabilization period, after a 10-min perfusion at the control PP (with or without halothane), just before initiating hypoperfusion, at 10, 20, and 30 min of hypoperfusion, and at 10, 20, 30, and 40 min of reperfusion at the control PP. Variables recorded at the end of each time period were spontaneous HR, AVCT, LVSP, positive and negative $dLVP/dt_{max}$, and halothane concentration. The type, incidence, and duration of atrial and ventricular dysrhythmias were monitored continuously. Both the dose of halothane and the levels of hypoperfusion were randomized. An additional group of control hearts (*n* = 8) was followed over the same time period without any experimental procedure.

Statistical differences among the control and the 0.74% and 1.65% halothane groups at each level of hypoperfusion were determined by two-way analysis of variance (Statview, Abacus Concepts, Calabasas, Calif., and CLR ANOVA, Clear Lake Research, Houston, Tex., software programs; MacIntosh SE30 computer, Apple Computer, Cupertino, Calif.). Differences among the 0%, 10%, and 25% hypoperfusion groups at each level of halothane and the respective control were also determined by two-way analysis of variance. Fisher's least significant difference test was used to compare means. The incidence of dysrhythmias was evaluated by χ^2-tests and their duration by unpaired *t*-tests. Mean values were considered significantly different at $P < 0.05$. All data are expressed as mean ± standard error of means (SEM).

Results

Coronary Flow

Coronary flow (control 5.6 ± 0.4 $mL \cdot min^{-1} \cdot g^{-1}$) decreased during hypoperfusion to 37%, 22%, and 0% at 25%, 10%, and 0% of the control PP (55 mm Hg), respectively, and was not affected by halothane.

Heart Rate and Atrioventricular Conduction Time

Initial control HR and AVCT were not different among the three perfusion groups. At the control PP, i.e., before hypoperfusion, 0.74% and 1.65% halothane significantly decreased HR (control 215 ± 5 beats/min) by 9% and 12%, respectively. Halothane (0.74% and

Table 1. Effects of Halothane on Heart Rate and Atrioventricular Conduction Time Before, During, and After Hypoperfusion

			Halothane			
PP (%)	Halothane (%)	Control	Before HP	30 min HP	10 min RP	40 min RP
Heart rate (beats/min)						
0	0	222 ± 4	222 ± 4	41 ± 5	221 ± 4	216 ± 6
	0.74	225 ± 7	203 ± 6^a	53 ± 16	199 ± 8^a	212 ± 6
	1.65	211 ± 6	186 ± 6^a	37 ± 9	193 ± 6^a	203 ± 6
10	0	207 ± 5	207 ± 5	54 ± 7	206 ± 4	206 ± 6
	0.74	208 ± 8	190 ± 9^a	86 ± 14	188 ± 9^a	194 ± 3
	1.65	203 ± 3	188 ± 4^a	64 ± 8	176 ± 5^a	194 ± 3
25	0	219 ± 6	219 ± 6	186 ± 7	218 ± 7	223 ± 9
	0.74	221 ± 6	195 ± 5^a	186 ± 9	202 ± 4^a	223 ± 4
	1.65	213 ± 6	188 ± 5^a	180 ± 9	188 ± 6^a	215 ± 6
AV conduction time (ms)						
0	0	59.4 ± 2	59.4 ± 2	AVB	63.3 ± 4	63.1 ± 2
	0.74	58.8 ± 1	60.5 ± 1	AVB	65.7 ± 2	60.6 ± 2
	1.65	61.0 ± 3	74.0 ± 4^a	AVB	82.0 ± 5^a	65.0 ± 2
10	0	59.7 ± 2	59.7 ± 2	AVB	63.8 ± 2	61.3 ± 2
	0.74	59.0 ± 2	60.6 ± 3	AVB	65.3 ± 4	58.7 ± 3
	1.65	60.6 ± 3	82.1 ± 2^a	AVB	92.1 ± 4^a	58.0 ± 3
25	0	58.3 ± 1	58.3 ± 1	77.9 ± 7	59.4 ± 2	61.1 ± 3
	0.74	58.0 ± 3	59.6 ± 3	79.5 ± 6	61.4 ± 4	60.9 ± 4
	1.65	57.9 ± 2	73.9 ± 4^a	73.9 ± 4	74.9 ± 4^a	59.8 ± 2

PP, perfusion pressure expressed as percentage from control perfusion pressure; control, values before exposure to 0%, 0.74%, or 1.65% halothane; before HP, values after exposure to 0%, 0.74%, or 1.65% halothane for 10 min and before the onset of hypoperfusion; RP, reperfusion; AVB, atrioventricular block.

All data are mean ± SEM.

^{a}$P < 0.05$ versus 0% halothane at each perfusion pressure.

1.65%) increased AVCT (control 59.2 ± 2.1 ms) by 2% (nonsignificant) and by 29.5%, respectively (Table 1).

On initiating hypoperfusion, atrial and ventricular bradycardia occurred and AVCT increased sharply in all nine groups. Second- and third-degree AV block followed in all hearts of the 0% and 10% hypoperfusion groups, and HR continued to decrease throughout the 30-min period of hypoperfusion so that atrial arrest and ventricular asystole occurred in the majority of the hearts in the 0% and 10% hypoperfusion groups. Because no heart remained in sinus rhythm in the 0% and 10% hypoperfusion groups after 30 min of hypoperfusion, AVCT could not be compared. In the 25% hypoperfusion group, HR progressively decreased and AVCT increased, but second-degree AV block occurred only in a few hearts.

On initiating reperfusion at the control pressure, HR was higher in the control group than in the halothane groups over the first 10 min of reperfusion. After 40 min of reperfusion there were no significant differences in HR and AVCT among the nine groups and no differences in HR and AV conduction from the initial controls. Administration of lidocaine to nonfibrillating hearts produced small and transient decreases in HR and LVSP and a small increase in AVCT; all these variables returned to their prelidocaine levels within 5 min.

Cardiac Rhythm

The major dysrhythmias during the 40-min period of reperfusion at the control pressure were ventricular tachycardia, ventricular fibrillation, and supraventricular tachycardia. Ventricular tachycardia occurred in 80% of hearts in the 0% PP and no halothane group, whereas 1.65% halothane significantly decreased the incidence of ventricular tachycardia to 37.5% in the 0% PP group (Figure 1). Halothane (1.65%) greatly decreased the duration of ventricular tachycardia from a control of 7.2 ± 3.3 min to 0.2 ± 0.1 min after PP at 0%, whereas 0.74% halothane did not significantly reduce the duration of ventricular tachycardia as compared with the no-halothane group. In the 10% PP group halothane did not significantly alter either the incidence or the duration of ventricular tachycardia. Ventricular tachycardia did not occur in any heart with reperfusion in the 25% PP groups.

Upon reperfusion after 0% PP, ventricular fibrillation occurred in all hearts in the control group. The

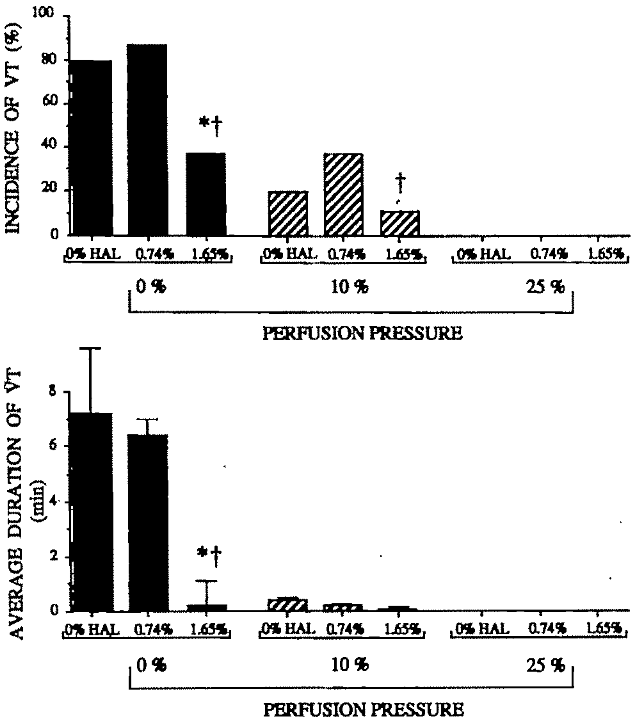

Figure 1. The effect of halothane on incidence (*top*) and average duration (*bottom*) of ventricular tachycardia (VT) during a 30-min period of reperfusion after 0%, 10%, and 25% PP. $^*P < 0.05$ vs control group. $†P < 0.05$ vs 0.74% halothane group (HAL).

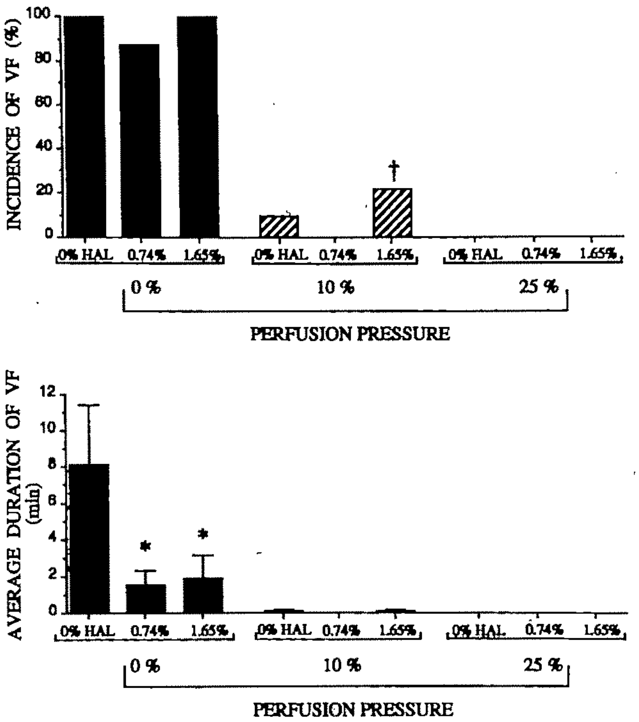

Figure 2. The effect of halothane on incidence (*top*) and average duration (*bottom*) of ventricular fibrillation (VF) during a 30-min period of reperfusion after 0%, 10%, and 25% PP. $^*P < 0.05$ vs control group. $†P < 0.05$ vs 0.74% halothane group (HAL).

incidence of ventricular fibrillation was not reduced in the halothane-treated group (Figure 2). However, the duration of ventricular fibrillation after 0% PP was significantly decreased from a control of 8.1 ± 3.3 min to 1.5 ± 0.8 min by 0.74% halothane and to 1.9 ± 1.2 min by 1.65% halothane. On reperfusion in the 10% PP groups, ventricular fibrillation occurred in 10% of control hearts and in 22% of hearts treated with 1.65% halothane. Halothane did not change either the incidence or the duration of ventricular fibrillation with reperfusion in the 10% PP group. Ventricular fibrillation did not occur at all with reperfusion in the 25% PP groups. The majority of the dysrhythmic hearts converted spontaneously either to sinus rhythm or to a less serious dysrhythmia. Lidocaine, given 30 min after reperfusion, converted all but three dysrhythmic hearts to sinus rhythm.

Supraventricular tachycardia occurred in the reperfusion period predominantly in halothane-treated hearts (Figure 3). Upon reperfusion after 0% PP, 1.65% halothane produced a significant incidence (37.5%) and duration (2.6 ± 2.5 min) of supraventricular tachycardia. On reperfusion after 10% PP, 0.74% halothane significantly increased the incidence of supraventricular tachycardia to 65% from the control value of 20%. However, 1.65% halothane did not alter the incidence of supraventricular tachycardia after hypoperfusion at 10% PP. The average duration of supraventricular tachycardia during the same time period was not significantly altered by halothane. In the 25% PP groups, the small incidence and duration of supraventricular tachycardia with reperfusion was not significantly different in the halothane-treated groups compared with their control groups.

Left Ventricular Pressure: Positive and Negative Pressure Derivatives

The mean left ventricular systolic pressures for the nine groups ranged from 96 ± 7 to 112 ± 6 with a mean of 103.6 ± 5 mm Hg (n = 85). There were no differences among the three halothane-free groups (mean 96 ± 7 mm Hg), the three 0.74% halothane groups (mean 102 ± 6 mm Hg), and the three 1.65% halothane groups (mean 112 ± 6 mm Hg). Before hypoperfusion and early in reperfusion there was a significant and dose-dependent decrease in LVSP while halothane was present.

With the onset of hypoperfusion, LVSP decreased in all groups; at PPs of 0% and 10%, contractions almost ceased and there was no difference in LVSP between halothane-free and halothane-treated

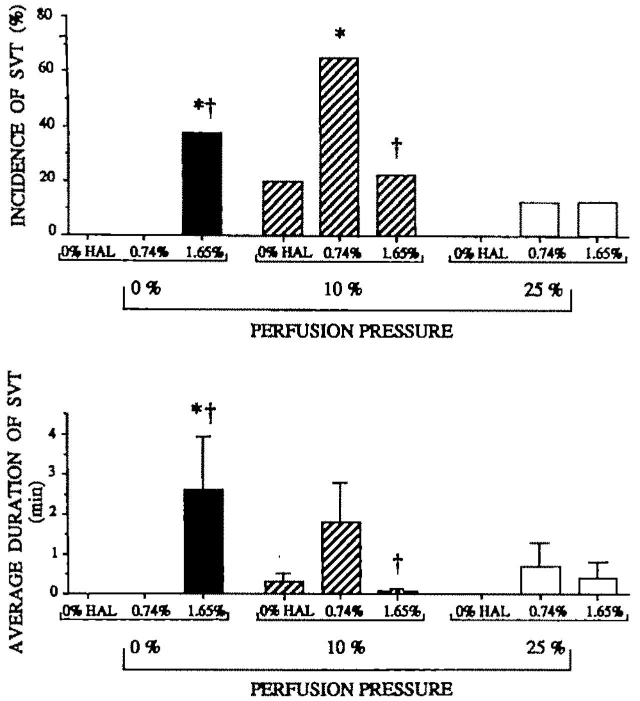

Figure 3. The effect of halothane on incidence (*top*) and average duration (*bottom*) of supraventricular tachycardia (SVT) during a 30-min period of reperfusion after 0%, 10%, and 25% PP. $^*P < 0.05$ vs control group. $^\dagger P < 0.05$ vs 0.74% halothane group (HAL).

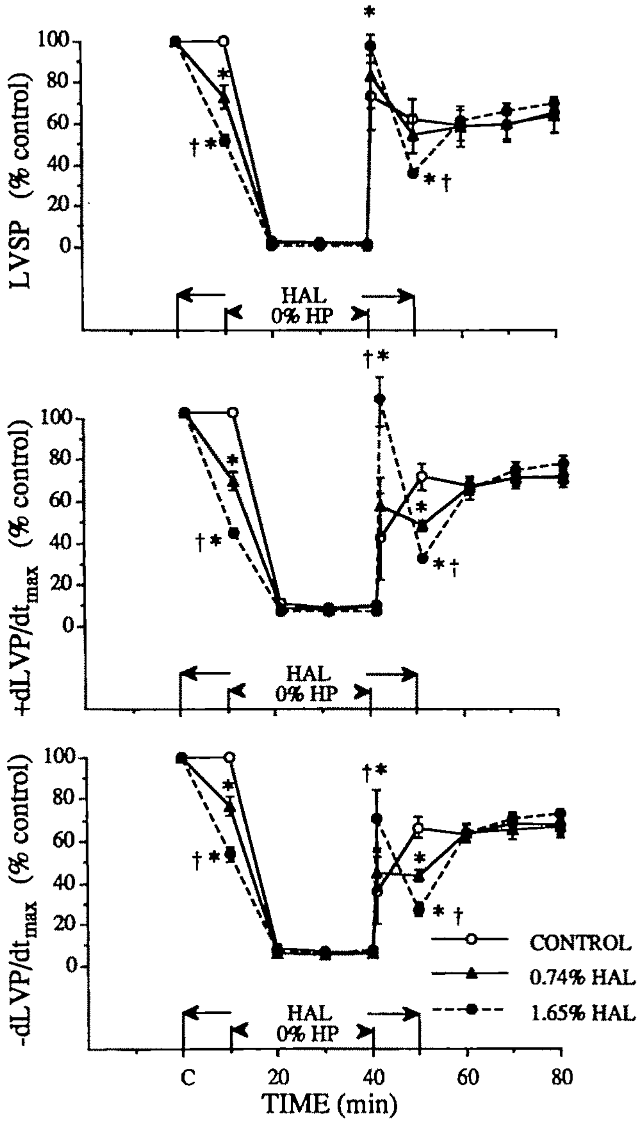

Figure 4. Percentage changes in systolic left ventricular pressure (LVSP) (*top*), positive dLVP/dt$_{max}$ (*middle*), and negative dLVP/dt$_{max}$ (*bottom*) before, during, and after global hypoperfusion (HP) (0% PP), in the absence (control) and presence of 0.74% and 1.65% halothane (HAL). Additional measurements of LVSP and dLVP/dt$_{max}$ were taken at the end of the first minute of reperfusion. $^*P < 0.05$ vs control group. $^\dagger P < 0.05$ vs 0.74% halothane group.

hearts. A smaller decrease in LVSP was observed during the 25% PP period, and this decrease was significantly greater in the 1.65% halothane-treated group than in the halothane-free group.

On reperfusion at the control perfusion pressure, LVSP increased in all groups. During the first minute of reperfusion, i.e., after 0% PP in the 1.65% halothane group, LVSP nearly reached the initial mean control value; in the halothane-free group, LVSP increased to about 75% of control. On reperfusion in the halothane-free groups, LVSP was higher in the 10% PP group than in the 0% PP group ($P < 0.05$), and higher in the 25% PP group than in the 10% PP group ($P < 0.05$) at 10, 20, 30, and 40 min after reperfusion. At 10 min of reperfusion, LVSP was significantly reduced by 1.65% halothane in the 0% PP group, but there was no significant difference in recovery of LVSP at the 40-min period of reperfusion among the halothane-free and halothane groups. The changes in LVSP at 20, 30, and 40 min of reperfusion after hypoperfusion at 0% or 10% PP were not significantly different from those observed in the halothane group (Figures 4 and 5 top). In none of the treatment groups was LVSP restored to the initial control value upon reperfusion. After 30 and 40 min of reperfusion following hypoperfusion at 25%, however, LVSP was significantly higher in the group treated with 1.65% halothane (Figure 6 top); in this group LVSP returned to 90% of control. In the time control group ($n = 8$) not subjected to hypoperfusion nor treated with halothane, LVSP decreased less than 7% from 99 ± 6 to 92.5 ± 9 mm Hg over the same time period (data not shown). This indicates that 1.65% facilitated recovery to a level no different than the time control.

Changes in positive and negative dLVP/dt$_{max}$ closely paralleled changes in LVSP in all groups as shown in Figures 4–6. An exception was that at 1 min of reperfusion in the halothane-free 0% PP group, the percent decreases in positive and negative dLVP/

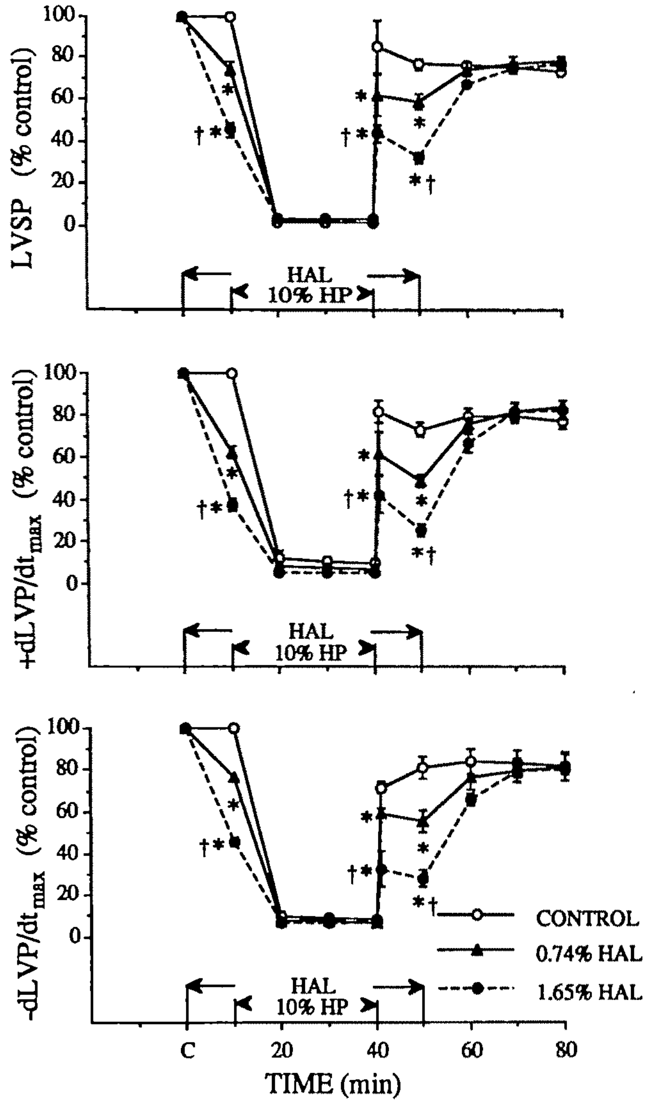

Figure 5. Percentage changes in systolic left ventricular pressure (LVSP) (*top*), positive dLVP/dt_{max} (*middle*), and negative dLVP/dt_{max} (*bottom*) before, during, and after hypoperfusion (HP) at 10% PP, in the absence (control) and presence of 0.74% and 1.65% halothane (HAL). Additional measurements of LVSP and dLVP/dt_{max} were taken at the end of the first minute of reperfusion. *$P <$ 0.05 vs control group. †$P < 0.05$ vs 0.74% halothane group.

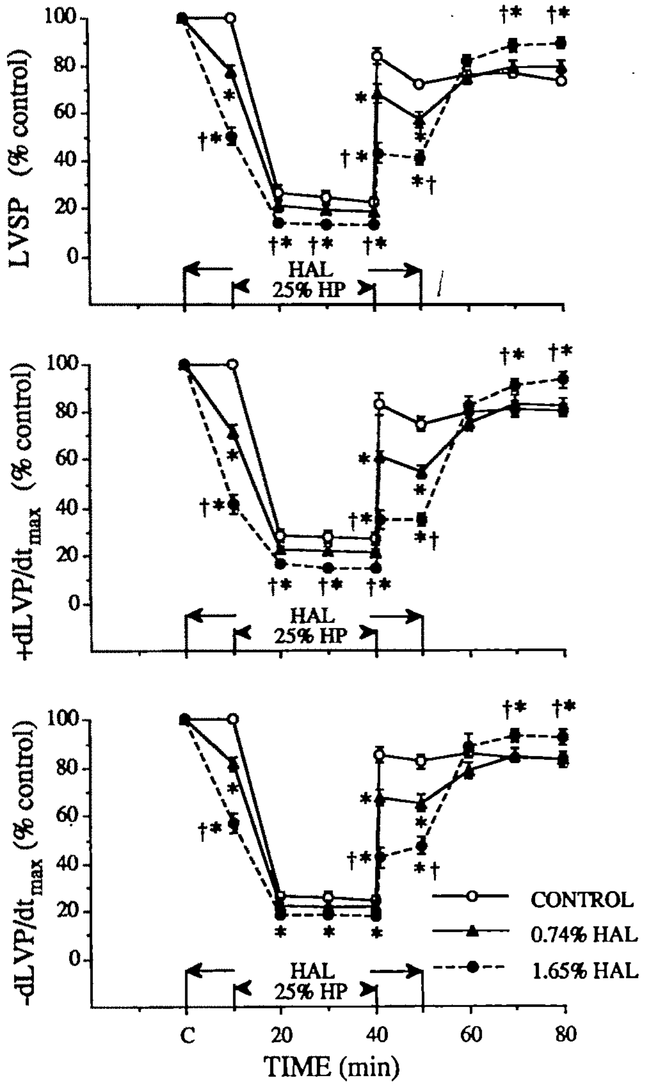

Figure 6. Percentage changes in systolic left ventricular pressure (LVSP) (*top*), positive dLVP/dt_{max} (*middle*), and negative dLVP/dt_{max} (*bottom*) before, during, and after hypoperfusion at 25% PP, in the absence (control) and presence of 0.74% and 1.65% halothane (HAL). Additional measurements of LVSP and dLVP/dt_{max} were taken at the end of the first minute of reperfusion. *$P <$ 0.05 vs control group. †$P < 0.05$ vs 0.74% halothane group.

dt_{max} were much greater than the corresponding decrease in LVSP.

Neither exposure to halothane nor hypoperfusion significantly altered left ventricular diastolic pressure (data not shown), which was initially set to 0 mm Hg by adjusting balloon volume. In the early reperfusion period, diastolic pressure increased only in the 0% PP groups. The average increase was 3 ± 1 mm Hg in the halothane-free groups and 7 ± 2 and 5 ± 2 mm Hg in the 0.74% and 1.65% halothane groups, respectively, after 10 min of reperfusion. However, this increase was only temporary, and diastolic pressure returned to the control level (0 mm Hg) in all groups by 30 min of reperfusion.

Discussion

We have examined the effects of halothane on cardiac injury resulting from global hypoperfusion and reperfusion. Injury was assessed by changes in rhythm and conduction, by depression of isovolumetric LVSP and its peak derivatives, and by the type, incidence, and duration of dysrhythmias. Our results indicate that halothane given before, during, and after a 30-min period of global hypoperfusion facilitates full recovery of contractile function after hypoperfusion at 25% perfusion pressure and greatly decreases the incidence and/or duration of ventricular tachycardia and fibrillation occurring during reperfusion after hypoperfusion at 0% and 10% PP. However, the presence of halothane induced supraventricular tachycardia in some groups.

In human or experimental coronary occlusion, a nonhomogeneous pattern of ischemia occurs so that a heterogeneous periinfarction zone exists wherein ischemia is less severe than in the central infarct. Our purpose was to assess the effects of halothane and the severity of the ischemic (gradual hypoperfusion) state on the resulting functional abnormalities. We used a model of short-term global hypoperfusion in which coronary PP can be precisely controlled at three levels below the control level. In our model of hypoperfusion, the three different levels of PP in the halothane-free groups differentially limited restoration of cardiac function. It seems probable that the more severe the hypoperfusion, the more severe is the reperfusion injury, as shown by the incidence and duration of reperfusion dysrhythmias and by improvement of contractile function.

The mechanisms of mechanical dysfunction and occurrence of dysrhythmias resulting from inadequate oxygen and substrate supply, from accumulation of metabolites during hypoperfusion, and from consequent reperfusion are still unclear. During ischemia there is a rapid decline in creatine phosphate and adenosine triphosphate, and a marked increase in inorganic phosphate, as the myocardium shifts from aerobic to anaerobic metabolism (25). Substantial increases in cytosolic-free sodium and calcium concentrations occur (26). When the ischemic heart is reperfused, there is massive entry of calcium into cells (27,28) with mitochondrial accumulation of calcium into dense intramitochondrial granules of calcium phosphate. The uptake of calcium is a feature of irreversible cellular injury and occurs during reperfusion (29). Deleterious changes may also include oxygen-free radical production, modification of membrane ionic currents, and inhibition of Na^+/Ca^{2+} exchange (30), calcium transporting ability (31), and Na^+/K^+ exchange (32), all of which can be expected to increase the susceptibility of the myocardium to electrophysiologic perturbations which in turn may promote the genesis of dysrhythmias.

It has been suggested that free radicals formed during ischemia or reperfusion produce deleterious effects by (a) peroxidizing cell membrane lipids, thus altering the structural integrity of the membrane, (b) peroxidizing the lipids involved in maintaining the microenvironment of membrane proteins, and/or (c) reacting both with proteins and with membrane lipids separately or concurrently (33). Oxidative stress occurs during reperfusion and depends on the severity of the ischemic period: the greater the degree of myocardial hypoperfusion, the greater is the rate of formation of free radicals on reperfusion (34).

Volatile anesthetics are potent negative chronotropic (35), dromotropic, and inotropic agents (36). Increasing evidence suggests that volatile anesthetics produce negative inotropic effects through mechanisms affecting many steps in the excitation-contraction process. Studies from our laboratory demonstrate that halothane decreases contractility of papillary muscle and decreases myoplasmic calcium concentration as measured by beat-to-beat changes in bioluminescence of aequorin, an indicator of free intracellular calcium (15). Using a single ventricular cell clamping technique, we also have shown that the decrease in intracellular free calcium with exposure to halothane is, at least in part, due to a decrease in calcium flux through voltage-dependent calcium channels (13). Moreover, halothane has been shown to reduce the accumulation of calcium after regional myocardial ischemia and after temporary depletion of calcium from the perfusate (calcium paradox) and to improve contractile function with reperfusion in isolated guinea pig hearts (16,17). We demonstrated recently that halothane improves myocardial function after global hypoxia and reoxygenation (19). All these studies suggest that halothane has at least one effect similar to that of calcium channel blockers, i.e., attenuation of the slow calcium current through voltage-dependent calcium channels. The calcium channel antagonists have been shown to protect against ischemia (37,38). Thus the effects of ischemia and reperfusion on calcium ion homeostasis play an important role in the cascade of events associated with irreversible myocardial injury.

The extent of cellular calcium overload is one of the major factors that determines the degree of dysfunction during reperfusion (39). The beneficial effects of reducing calcium in the coronary perfusate during early reperfusion may be attributed to reduced calcium overload through Na^+/Ca^{2+} exchange rather than to improved energy metabolism (39). Extracellular calcium concentration can influence vulnerability to reperfusion-induced arrhythmias because protection has been afforded by reducing calcium accumulation during ischemia and reperfusion (40). Halothane has been demonstrated to produce significant antifibrillatory activity in a canine acute coronary artery occlusion/reperfusion model (18).

We have recently reported in isolated hearts that halothane improves the oxygen supply to demand ratio by decreasing cardiac work and oxygen extraction rather than by increasing oxygen delivery (41). Similar results were found in a different experimental model (42). During and after perfusing hearts at 25% of the control pressure, halothane might serve to protect against hypoperfusion-induced injury by decreasing myocardial oxygen consumption, as shown by the reduction in contractile function observed during hypoperfusion. This protective effect of halothane, however, was not observed during reperfusion in the 0% and 10% PP groups, even though there was a small difference in contractile function of these groups during reperfusion.

There was a significant increase in LVSP and $+dLVP/dt_{max}$ during the first min of reperfusion only in the 0% PP group given 1.65% halothane compared with the 0% control group. The cause for this phenomenon is unclear. It is not related, however, to differences in coronary PP or coronary flow during the period of reactive hyperemia after resumption of coronary perfusion. One possibility is that at 1 min of reperfusion there was a lesser accumulation of byproducts of metabolism, as well as sodium and calcium, in this group given halothane before total coronary occlusion compared with the 10% and 25% PP groups. On reperfusion in the 25% PP groups, contractile function improved more in the 1.65% halothane group than in the halothane-free control group after 40 min of reperfusion. This suggests a protection by halothane on recovery of mechanical function after moderate (25%) but not severe (0% and 10%) hypoperfusion. The greater recovery of contractile function in the halothane group could reflect protection by halothane through a decrease in oxygen demand rather than through an increase in oxygen supply. Additional protection could be afforded by an induced decrease in heart rate by halothane. Halothane, in a nonglobal cardiac ischemic model, has been shown to improve oxygen balance in ischemic as compared with nonischemic areas of myocardium (43).

Although the major mechanism for cardiac protection may be due to a direct effect on decreasing accumulation of calcium before, during, and after hypoperfusion, as we have previously reported (16,17), an additional protective mechanism of halothane may be through its effect on decreasing heart rate, as heart rate is a determinant of the oxygen supply-to-demand ratio. The protective effect of a lowered heart rate against dysrhythmias occurring during reperfusion has been demonstrated in isolated rat hearts (44). An increase in heart rate has been shown to increase the severity of ischemic injury (45) and also to increase the incidence of reperfusion dysrhythmias (38).

Halothane has been suggested to have both prodysrhythmic and antidysrhythmic effects. Disturbances in automaticity and conduction caused by halothane can lead to cardiac dysrhythmias. We have previously reported that halothane diminishes changes in the refractory period of ventricular muscle fibers induced by hypercarbia (46) and that halothane decreases the spontaneous rate of Purkinje fibers surviving in the ischemic region of canine heart infarcted 24 h earlier (47).

In the 0% and 10% PP groups no heart remained in the sinus rhythm making it impossible to measure AVCT. Endogenously released adenosine is at least partially responsible for the increase in AVCT during hypoxia (48) and possibly during ischemia. Although sinoatrial and AV nodal rates were dramatically altered during ischemia, the complete recovery of heart rate and AVCT with reperfusion is consistent with the relative resistance of nonworking specialized nodal fibers to structural damage caused by global ischemia and reperfusion (46,49).

The halothane-free groups exhibited a shorter time in sinus rhythm and a longer time in dysrhythmic patterns. The antidysrhythmic effect observed with halothane persisted not only during exposure to halothane during early reperfusion but also after discontinuation of halothane, because the 0% and 10% PP groups exhibited a lesser duration of dysrhythmias 30 min after halothane was discontinued. A possible explanation is that halothane attenuates damage to the conduction system or myocardial Purkinje cells, which have a potential for abnormal automaticity secondary to hypoperfusion and reperfusion.

In the current study, halothane produced supraventricular tachycardia with reperfusion at each level of reduced PP, and the incidence and duration of supraventricular tachycardia was greater at the two lower PPs. This prodysrhythmic effect of halothane was concentration-independent, and it was altered by the level of hypoperfusion. As shown in the current study and in our previous studies (24,50), halothane decreases automaticity of sinoatrial and AV nodes and conduction through intraatrial and intraventricular tissue and increases AV nodal refractoriness (51). The reentry mechanism might be involved in the occurrence of supraventricular tachycardia. Also, isolated ischemic hearts exhibit enhanced catecholamine release (52), which might interact with halothane to cause rhythm disturbances, possibly due to enhanced automaticity in subsidiary atrial pacemakers (53). Apparently, this prodysrhythmic effect of halothane is associated with ionic and metabolic changes occurring during hypoperfusion and reperfusion in atrial tissue. Atrial tissue may also differ from ventricular tissue in some electrophysiologic properties involved in the genesis of dysrhythmias.

Overall, our in vitro study suggests that halothane may directly ameliorate the degree of dysfunction induced by global hypoperfusion and reperfusion under certain experimental conditions. The underlying mechanism could be due to decreased myoplasmic accumulation of calcium during reperfusion, decreased metabolic requirements for oxygen afforded by halothane before, during, and after reperfusion, or by both. Although during the reperfusion period there was no difference in recovery of contractile function with halothane in the 0% and 10% PP groups, there was a difference in electrophysiologic recovery. The incidence and duration of serious ventricular dysrhythmias, which were much more severe in the 0% PP group, were reduced by halothane. It appears that even at a PP of 10% of control, there is sufficient delivery of oxygen and nutrients and wash out of generated free radicals and other metabolic by-products to afford beneficial electrophysiologic effects because there were fewer dysrhythmias. But halothane may significantly improve contractile function only when coronary pressure and flow are better maintained, i.e., as in the 25% PP group. With cessation or near cessation of flow, halothane appears to offer no added protection of contractile function during reperfusion, but does appear to have beneficial electrophysiologic effects on the basis of reduced dysrhythmias. Global hypoperfusion of increasing duration in vivo would, of course, have more serious sequelae because, as hypotension occurs and coronary flow decreases, death would result from intractable dysrhythmias and cardiac standstill. However, the relative increase in the oxygen supply-to-demand relationship, or the calcium flux effects, afforded by halothane before the onset and during hypoperfusion could be beneficial in improving myocardial function with reperfusion.

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Propofol and Thiopental Depression of Myocardial Contractility

A Comparative Study of Mechanical and Electrophysiologic Effects in Isolated Guinea Pig Ventricular Muscle

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The purpose of the study was to compare the actions of propofol and thiopental on myocardial contractility and cellular electrophysiologic behavior. Isometric tension of isolated guinea pig right ventricular papillary muscle was studied in normal and 26 mM potassium Tyrode's solutions at various stimulation rates (after rest up to 3 Hz). Normal and slow action potentials were also recorded by conventional microelectrodes. Propofol (30, 100, and 300 μM) applied in the commercial 10% Intralipid emulsion caused dose-dependent depression of contractions at all stimulation rates, whereas Intralipid alone had no effect. Thiopental (10, 30, and 100 μM) caused depression similar to the threefold greater concentrations of propofol. Although neither drug altered the normal action potential (AP) amplitude or dV/dt max, thiopental (30 μM) increased AP duration. In the partially depolarized (26 mM potassium) β-adrenergically stimulated myocardium, propofol and thiopental caused dose-dependent contractile depression similar to that in normal Tyrode's solution. Whereas propofol did not alter slow AP characteristics, 30–100 μM thiopental increased slow AP duration (consistent with decreased potassium conductance), and 100 μM thiopental depressed dV/dt max (consistent with decreased calcium channel ionic influx). Comparing the clinical plasma concentration ranges required for an equivalent anesthetic effect, propofol depresses myocardial contractility less than thiopental.

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By virtue of its rapid onset, short duration of action, and rapid elimination, propofol (2,6-diisopropylphenol) would appear to be an attractive alternative to thiopental for induction of anesthesia (1,2). Yet induction of anesthesia with propofol in patients is often associated with a decrease in systemic arterial pressure (3–9). These previous clinical studies on the hemodynamic effects of anesthetic induction with propofol have provided conflicting results with regard to effects on cardiac output and systemic vascular resistance (SVR). In animal models, several authors have reported that the decrease in arterial blood pressure after administration of propofol is caused by a decrease in cardiac output associated with little change (10) or a decrease (11,12) in SVR. Whereas some results implicate depression of myocardial contractility as contributing to the decrease in systemic arterial pressure after propofol administration (9,10,12–14), other studies suggest that decreased arterial blood pressure is caused by a reduction in cardiac output owing to venodilation and diminished preload (4,6,14–17), or owing primarily to decreased SVR without depression in cardiac output or stroke volume (3,4,7,16,18).

In view of these conflicting observations, we determined the direct negative inotropic effect of clinical concentrations of propofol and compared these effects to those produced by clinical concentrations of thiopental in the same isolated myocardial preparation. A variety of inotropic interventions were used to provide mechanistic insights, and drug actions on cellular electrophysiologic behavior were also compared.

Methods

According to a protocol approved by the University of Virginia Animal Research Committee, the heart was removed from female guinea pigs (300–400 g)

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under methoxyflurane anesthesia, and right ventricular papillary muscles were isolated. Control studies demonstrate no residual action of the methoxyflurane in the myocardium. The excised muscle was mounted horizontally in a tissue bath, and the tendinous end was attached by a strut to a Grass FT03 force transducer. Muscle length was adjusted to the lowest resting tension at which maximum twitch tension was observed. The bath was superfused at 37°C at a rate of 8 mL/min throughout the experiment with modified Tyrode's solution composed of 143 mM Na, 5 mM K, 121 mM Cl, 1.2 mM $MgSO_4$, 25 mM HCO_3^-, 11 mM glucose, and 0.1 mM ethylenediaminetetraacetic acid. This solution was circulated through the bath from reservoirs (37–38°C) through which 95% O_2/5% CO_2 was bubbled maintaining pH at 7.45 ± 0.5. Muscles were field-stimulated by stimuli of 0.5-ms duration through a pair of stainless steel electrodes along the wall of the bath. Membrane potential (V_m) was monitored by a conventional 3 M KCl-filled glass microelectrode (10–20 MΩ) attached to a WPI VF-1 preamplifier. Tension, V_m, and its rate of change during the action potential (dV/dt) were monitored on digital storage oscilloscopes, and tension, its differentiated signal (dT/dt), and V_m were continuously recorded on a Gould Brush 2400 recorder.

After 15 min of rest, a rested-state contraction was elicited followed by stimulation rates of 0.1, 0.25, 0.5, 1, 2, and 3 Hz applied sequentially. Each stimulation rate was maintained until an unchanging, steady state contraction was achieved, before proceeding to the next higher frequency. In normal Tyrode's solution, increasing the stimulation rate resulted in a typical "positive staircase"; contractions at 2–3 Hz were 10–20-fold greater than those after rest, similar to previous results from this laboratory with this preparation (19,20). After control studies, muscles were exposed to each drug for 15 min before the recording of responses. In control experiments, a 15-min application of drug was sufficient to cause a stable and unchanging effect. Recovery responses were recorded after washout of drug for 20–25 min. After each experiment, the cross-sectional area of each muscle was calculated from the muscle length, weight, and density (1.04 g/mL) assuming a cylindrical form. In the tension studies, cross-sectional area ranged from 0.18 to 1.26 mm^2 in the muscles studied, with a mean cross-sectional area of 0.53 ± 0.24 mm^2 (mean ± SD, $n = 34$). Intracellular impalement was attempted in most muscles; however, higher stimulation rates (2 and 3 Hz) frequently caused dislodgement of impaled microelectrodes. Only results from an impalement that was maintained throughout the whole sequence (i.e., control, drug exposure, and washout periods) were tabulated. Stimulation intensity was maintained at ~110% of the lowest level necessary to elicit a response and then adjusted during the experiment to maintain approximately the same latency (stimulus-action potential interval, usually 5–10 ms) at all stimulation rates. Action potential (AP) amplitude, maximum rate of depolarization (dV/dt max), and AP duration at 50% and 95% repolarization (APD_{50} and APD_{95}, respectively) were measured.

Muscle tension and action potentials were also studied in muscles in 26 mM K^+ Tyrode's solution (122 mM Na, 26 mM K, 121 mM Cl, 1.2 mM $MgSO_4$, 25 mM HCO_3^-, 11 mM glucose, and 0.1 mM ethylenediaminetetraacetic acid), which caused partial depolarization to −40 to −45 mV and inactivated fast sodium channels. β-Adrenergic stimulation with 0.1 μM isoproterenol increases the number of Ca^{2+} channels that can be activated, thus permitting slow action potentials, increasing extracellular Ca^{2+} entry, and enhancing contractility (21). The increased cyclic adenosine monophosphate owing to β-adrenergic stimulation also promotes Ca^{2+} uptake into the sarcoplasmic reticulum (SR) (22,23). The sequential increase in stimulation rate after rest was performed as in the 5 mM K^+ Tyrode's solution. The pattern of tension after rest and up to 0.5–1-Hz stimulation consistently demonstrated a distinct late phase of tension development (24); the rate of tension development after rest up to 0.5–1 Hz showed distinct early and late maxima, termed dT_E/dt max and dT_L/dt max, respectively (19,25). Late peaking tension was not present at 2 and 3 Hz, and no value of dT_L/dt max was noted. Action potential characteristics (amplitude, dV/dt max, APD_{50}, and APD_{95}) were determined as in 5 mM K^+ Tyrode's solution. Owing to the difficulty of maintaining intracellular impalements and appropriate stimulus-AP latencies at 2- and 3-Hz stimulation, accurate measurements for slow AP dV/dt max could be reliably recorded only up to 1 Hz.

An additional series of muscles was also studied in Tyrode's solution with Na^+ reduced to 40 mM, replacing 100 mM NaCl with 200 mM sucrose to maintain osmolarity. By reducing the Na^+ gradient across the cell membrane, the driving force for the Na-Ca exchange is reduced, so that the sarcoplasmic reticulum stores of Ca^{2+} are not reduced and remain full during rest. Stimuli after rest, at 0.01 or 0.1 Hz, show very strong contractions with rapid tension development, similar to those seen with 2–3-Hz stimulation in normal Tyrode's solution.

Papillary muscle experiments performed are outlined in Table 1. Increasing concentrations of propofol (30, 100, and 300 μM; or 5.3, 17.8, and 53 μg/mL) and thiopental (10, 30, and 100 μM; or 2.6, 7.9, and 26.4 μg/mL) were applied sequentially to muscles to assess each drug effect. Propofol at various concen-

Table 1. Experiments Performed With Sequence of Solutions Applied

I. Force-frequency studies, rested state up to 3 Hz
  A. In standard Tyrode's solution
    1. Control, Tyrode with 0.018% Intralipid emulsion, 100 μM propofol emulsion, washout with Tyrode–0.018% Intralipid
    2. Propofol dose response (control, 30, 100, 300 μM, washout)
    3. Thiopental dose response (control, 10, 30, 100 μM, washout)
  B. In 26 mM K$^+$ Tyrode's solution with 0.1 μM isoproterenol
    1. Control, Tyrode–0.018% Intralipid, 100 μM propofol emulsion, washout with Tyrode–0.018% Intralipid
    2. Propofol (control, 30, 100, 300 μM, washout)
    3. Thiopental (control, 10, 30, 100 μM, washout)
II. Action potential studies, 0.1–1 Hz
  A. Normal action potentials in standard Tyrode's solution
    1. Control, Tyrode–0.018% Intralipid, 100 μM propofol emulsion, washout with Tyrode–0.018% Intralipid
    2. Thiopental (control, 30 μM, washout)
  B. Slow action potential studies in 26 mM K$^+$ Tyrode's solution with 0.1 μM isoproterenol
    1. Control, Tyrode–0.018% Intralipid, 100 μM propofol emulsion, washout with Tyrode–0.018% Intralipid
    2. Thiopental (control, 30 μM, washout)
    3. Thiopental (control, 100 μM, washout)
III. Experiments in low-Na Tyrode's solution, 0.01 and 0.1 Hz
    1. Propofol (control, 100, 300 μM, washout)
    2. Thiopental (control, 30, 100 μM, washout)

trations was applied in its commercially available 10% Intralipid emulsion (56 mM [10 mg/mL] propofol, 10% soybean oil, 2.25% glycerol, and 1.2% purified egg phosphatide). In a number of experiments, before and subsequent to 100 μM propofol application, Intralipid by itself was applied in a concentration (0.018%) equivalent to that which would be obtained with emulsion sufficient for 100 μM propofol.

Repeated measures analysis of variance (ANOVA) followed by Scheffe's multiple range test was applied to test for significant differences among the stimulation rates and among the drug concentrations. A P value < 0.05 was considered adequate to indicate significant differences. The dose dependence of contractile depression was fit by a simple regression versus the log of drug concentration, and the 90% and 95% confidence intervals of slope were determined (Statview Software, Abacus Concepts, Inc.).

Results

Experiments With Normal Tyrode's Solution

Administered in a concentration equivalent to 100 μM propofol, Intralipid emulsion (0.018%) alone had no depressant action (Figure 1A). The same emulsion including propofol (100 μM) depressed peak tension (upper panel) and dT/dt max (lower panel) at all stimulation rates. Washout of drug caused substantial reversal of the effect at the higher stimulation rates. As the action of Intralipid alone was negligible, the effects of 30, 100, and 300 μM propofol (as emulsion) were compared with standard Tyrode's solution control (Figure 1B). Propofol dose-dependently depressed contractions, with effects at 100 and 300 μM being greater ($P <$ 0.05, ANOVA) than effects at 30 and 100 μM, respectively. The magnitude of depression with 100 μM propofol was similar to that observed with the Intralipid pretreatment. Washout of the 300 μM propofol effect restored contractility to ~40% of control levels (data not plotted for clarity). Dose-dependent contractile depression by thiopental (10, 30, and 100 μM) was roughly equivalent to that caused by the threefold greater concentrations of propofol (Figure 1C). Contractile depression at 2–3 Hz was greater than that at 0.5–1 Hz for all thiopental concentrations. In normal action potential experiments, Intralipid and 100 μM propofol caused no change in normal AP amplitude, dV/dt max, APD_{50} and ADP_{95} with mean AP characteristics at 0.5 Hz shown in Table 2. The equivalent contractile depressant dose of thiopental (30 μM) did not depress AP amplitude and dV/dt max, but APD_{50} and APD_{95} were prolonged at 0.5 Hz (Figure 2A, Table 2), an effect seen at all stimulation rates. There was also a tendency for the muscles to depolarize slightly in 30 μM thiopental: resting V_m increased from -83.5 ± 3.0 mV (mean of control and recovery) to -79.3 ± 3.3 mV ($P = 0.099$ by paired t-test).

Experiments With High-K$^+$ Tyrode's Solution

In 26 mM K$^+$ Tyrode's solution with 0.1 μM isoproterenol, contractions after rest and up to 0.5–1 Hz showed a typical late-peaking response (Figure 3). As in normal Tyrode's solution, Intralipid (0.018%) had no effect on contractions, whereas subsequent 100 μM propofol emulsion depressed peak tension with greater depression of dT_L/dt max than of dT_E/dt max (not shown). With sequential application, 30 μM propofol had little effect, whereas 100 and 300 μM propofol depressed peak tension at all stimulation rates (Figure 4A). Propofol depression of the late tension was most prominent (see Figures 3A and 4A): dT_L/dt max was ~10% of control in 300 μM propofol ($\leq$1 Hz); dT_E/dt max was depressed by only 50%–60%.

Thiopental also caused dose-dependent depression of peak tension of slow AP contractions, especially from rest up to 1 Hz. Similar to effects of 300 μM propofol, 100 μM thiopental decreased late tension (dT_L/dt max) to 5%–10% of control, while decreasing early tension (T_E/dt max) to about 40% of control.

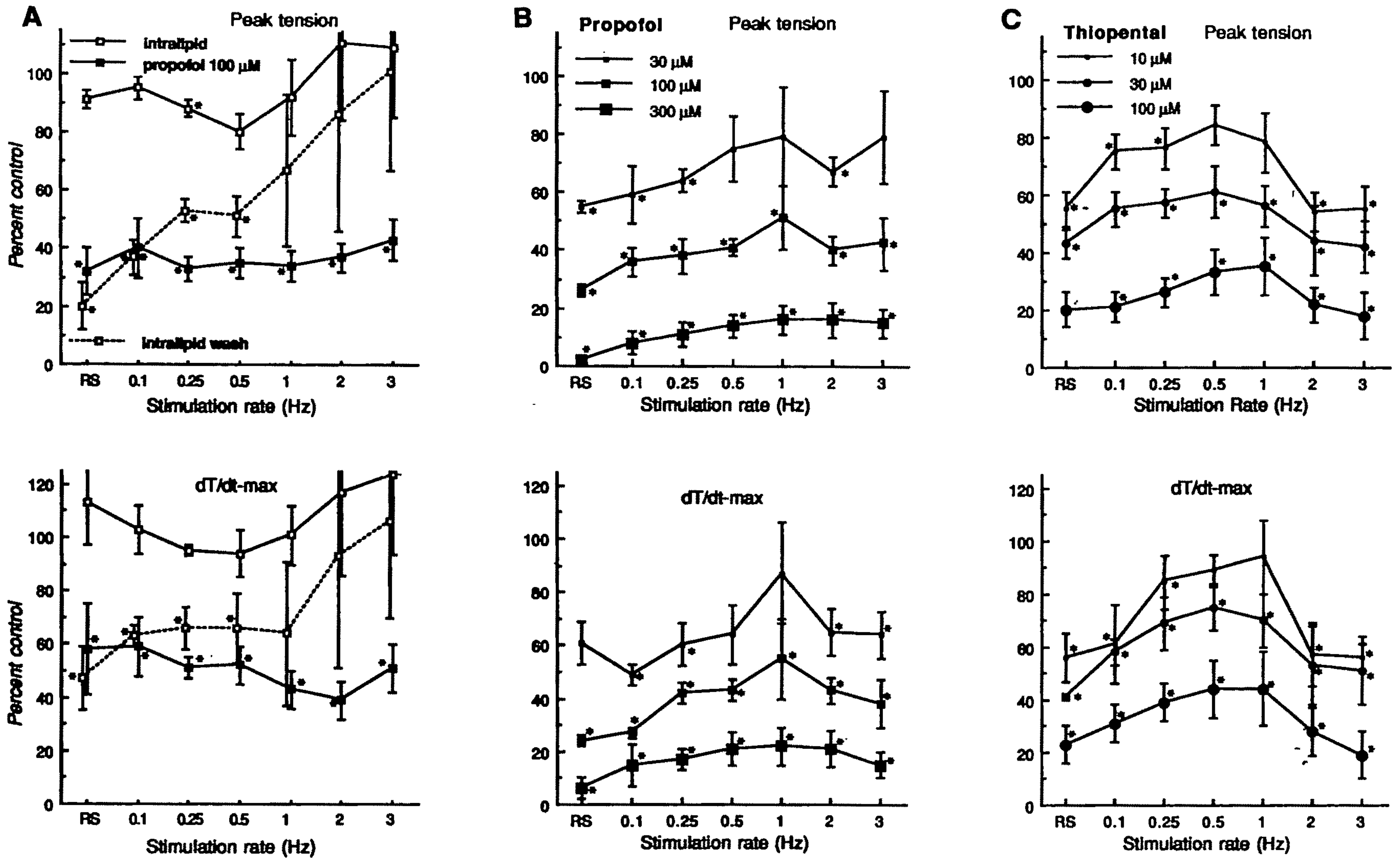

Figure 1. Effects of propofol and thiopental on myocardial contractions in standard Tyrode's solution at various stimulation rates. Results are plotted as mean (±SEM) percent of control (n = 5–7). *Upper panels* show actions on peak tension and *lower panels* show alteration in maximum rate of tension development (dT/dt max). *Difference ($P < 0.05$) from control. A. Effects of 100 µM propofol (with 0.018% Intralipid) or of prior and subsequent application of equivalent Intralipid (0.018%) alone. B. Effects of increasing concentrations of propofol (added as Intralipid emulsion). At each stimulation rate, depression by 100 and 300 µM propofol was greater than with 30 and 100 µM, respectively (repeated measures ANOVA). C. Effects of increasing concentrations of thiopental. Depression by 30 µM was greater than 10 µM thiopental at 0.1–0.25 Hz, and 100 µM caused greater depression than 30 µM at all stimulation rates.

Table 2. Effects of 100 μM Propofol and 30 μM Thiopental on Normal Action Potential Characteristics at 0.5 Hz

	Amplitude (mV)	dV/dt max (V/s)	APD_{50} (ms)	APD_{95} (ms)
Propofol 100 μM				
Control	115 ± 1	242 ± 32	161 ± 5	187 ± 6
Intralipid	115 ± 2	293 ± 23	161 ± 5	195 ± 8
Propofol	119 ± 3	248 ± 15	156 ± 8	192 ± 11
Washout	116 ± 3	268 ± 2	154 ± 4	191 ± 31
Thiopental 30 μM				
Control	125 ± 3	289 ± 28	153 ± 8	187 ± 10
Thiopental	122 ± 3	267 ± 33	166 ± 11*	214 ± 12*
Washout	125 ± 3	277 ± 44	156 ± 11	190 ± 13

Values represent mean ± SEM for nine experiments. Repeated measures analysis of variance followed by Scheffe's multiple range test was used to test for difference among groups.

*$P < 0.05$ differed from control and washout values.

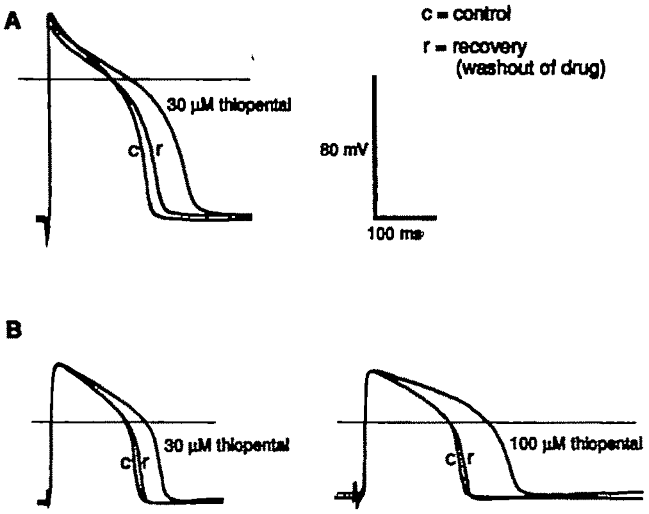

Figure 2. Effects of thiopental on cardiac action potentials (APs). The *horizontal line* indicates 0 mV. **A.** Effects of 30 μM thiopental on normal APs recorded at 0.5 Hz stimulation rate. **B.** Effects of 30 and 100 μM thiopental on slow APs recorded at 1 Hz stimulation rate in 26 mM K^+ Tyrode's solution with 0.1 μM isoproterenol. Stimulation intervals of longer than 1.6 s resulted in spontaneous APs in 100 μM thiopental.

Partial recovery was observed with washout of the 100 μM thiopental, the final recovery contractions being similar to those seen in 10 μM thiopental (not plotted for clarity).

Neither Intralipid nor 100 μM propofol caused any changes in the slow AP amplitude, dV/dt max, and APD_{50} and APD_{95}. In contrast, 30 and 100 μM thiopental caused a reversible, dose-dependent AP prolongation of 15%–33%, depending on stimulation rate and dose (Figures 2B and 5). Automaticity developed in all four muscles in 100 μM thiopental, either 5–10 min after exposure or at the beginning of thiopental washout. The automatic pattern had a regular rate of ~0.7 Hz (40 beats/min), so stimulated slow APs were characterized only at 1 Hz: dV/dt max decreased from 22 ± 2 to 19 ± 1 V/s (recovery: 23 ± 1 V/s); APD_{50} increased from 113 ± 3 to 153 ± 6 ms (recovery: 128 ± 3 V/s); APD_{95} increased from 131 ± 2 to 188 ± 6 ms (recovery: 150 ± 4 V/s). Automaticity was unaltered after overdrive pacing at 2–3 Hz, but resolved 2–4 min after drug washout. In 2 of 4 experiments, 100 μM thiopental application caused a depolarization of 2–5 mV. After an AP, V_m repolarized to near the untreated level, and then gradually depolarized (see Figure 2B), resulting in a spontaneous AP if the stimulation interval exceeded 1.6–1.7 s.

Effects in Low-Na^+ Tyrode's Solution

Propofol (100 and 300 μM) and thiopental (30 and 100 μM) depressed contractions in 40 mM Na^+ Tyrode's solution in a degree similar to their depression of rapid tension development at 2–3 Hz in other Tyrode's solution (Table 3). At identical stimulation rates, either dose of propofol or thiopental tended to depress dT/dt max somewhat less than the peak tension. Whereas depressant effects of the lower drug doses did not differ, 100 μM thiopental was more depressant on 0.01 Hz contractions than was 300 μM propofol.

Discussion

Several authors (3,4,7) have reported that decrease in arterial blood pressure after administration of propofol is caused by a decrease in systemic vascular resistance (SVR) with little or no change in cardiac output or stroke volume. Other studies suggest that the reduction in arterial blood pressure after propofol is related primarily to venodilation, resulting in decreased pulmonary capillary wedge pressure and a subsequent decrease in cardiac index, with SVR decreasing or remaining unchanged (6,15,17). However, Van Aken et al. (5) found major hemodynamic depressant effects of propofol on cardiac output and stroke volume with only minor effects on SVR. Several other reports from both clinical and animal studies (7,9–12,26), as well as recent in vitro reports (27–29), suggest that propofol caused some degree of myocardial depression in addition to any vasodilating effect.

In the present study, the ~50% depression of tension development at 2–3 Hz by 100 μM propofol is identical to the 50% depression caused by 112 μM (20 mg/L) propofol in rabbit papillary muscle at 2 Hz and 30°C (29). Similarly, in a previous guinea pig papillary muscle study, propofol had a calculated

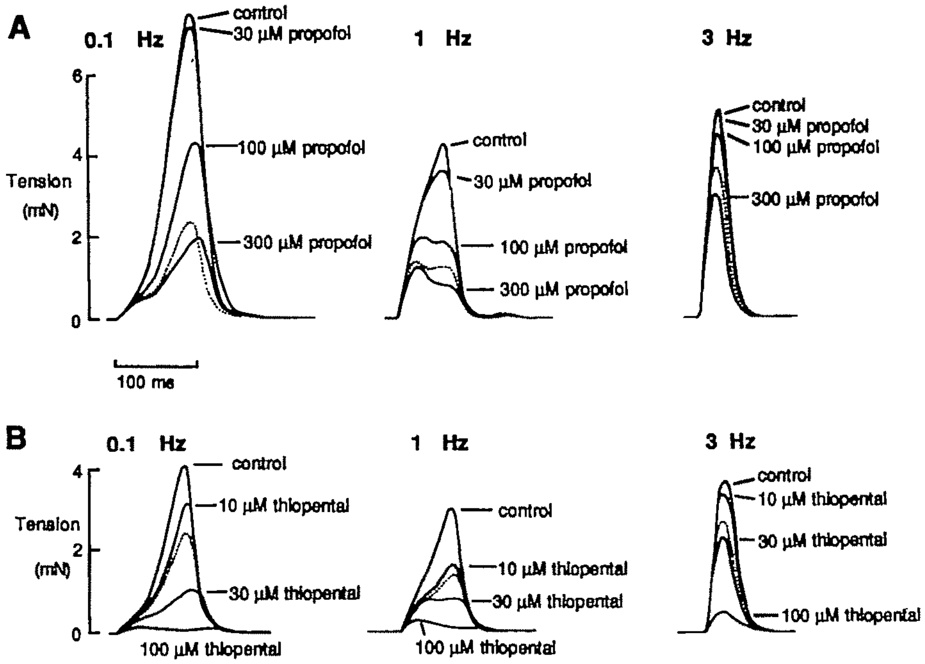

Figure 3. Depression by propofol and thiopental of papillary muscle contractions elicited in 26 mM K^+ Tyrode's solution with 0.1 μM isoproterenol. Contractions, which accompanied slow action potentials, are shown for 0.1-, 1-, and 3-Hz stimuli. *Dotted line* indicates response after drug washout for 20 min. **A.** Effects of 30, 100, and 300 μM propofol. **B.** Effects of 10, 30, and 100 μM thiopental.

IC_{50} of 78 μM for 1-Hz contractions at 35°C (28). These in vitro results are in agreement with the findings in the open-chest pig model, where a significant correlation existed between the propofol concentration (≤12 μg/mL or ≤67 μM) and up to a 50% decrease in myocardial contractility as assessed by the end-systolic pressure-length relationship (10). It is noteworthy in that study that myocardial depression did not reverse with the decline in serum concentration. Such lack of rapid reversibility was observed in this study as well as in a recent report in isolated rabbit septum in which 170–350 μM propofol caused 50% depression of contractility (27). The highly hydrophobic nature of propofol (octanol/water partition of ~5000 [Professional Communication, Medical Information, ICI Pharmaceuticals Group, Wilmington, Del.]) may slow its washout into aqueous media.

Myocardial depression by thiopental has been previously reported by a number of investigators. Price and Helrich (30) described the depression of contractility in the dog heart-lung preparation. They found the 50% depressant concentration to be 3.5 mg% (133 μM). Effendi et al. (31) observed 50% of control tension with 190 μM and 259 μM thiopental in the isolated newborn and adult guinea pig heart, respectively, using a Langendorff preparation stimulated at 4 Hz and 37°C. Davies and McCans (32) found that the tension of whole perfused rabbit heart at 37°C was depressed to 40% of control by 400 μM thiopental at 1 Hz, which decreased to 30% of the control values at 2.5 Hz. In contrast, isolated excised heart muscle is depressed by lower thiopental concentrations. Frankl and Poole-Wilson (33) reported that 28 and 227 μM thiopental reduced the developed tension by 50% and 80%, respectively, in an arterially perfused intraventricular septum of the rabbit. Komai and Rusy (34) observed that 10, 20, and 30 mg/L thiopental (29, 58, and 87 μM) depressed rabbit papillary (at 30°C) muscle peak contractile force at 1 Hz to 77%, 58%, and 44% of control, respectively, and contractions at 2 Hz to 76%, 55%, and 35% of control. These observations in excised myocardial muscle preparations are very similar to the dose dependence of depression by thiopental in the present study. In addition, the somewhat greater percentage depression of contractility at higher stimulation rates in normal Tyrode's solution was a finding of the present and prior studies.

The contractile dose response observed in this study and in normal Tyrode's solution at 3 Hz is shown in Figure 6. The regression lines for the dose dependence of contractile depression did not vary between the two drugs, although at least a threefold higher concentration of propofol was required to obtain the same degree of depression observed with thiopental. The lower drug concentrations studied represent the serum levels anticipated clinically. A 6-mg/kg intravenous bolus injection of thiopental in patients gives an average peak concentration in se-

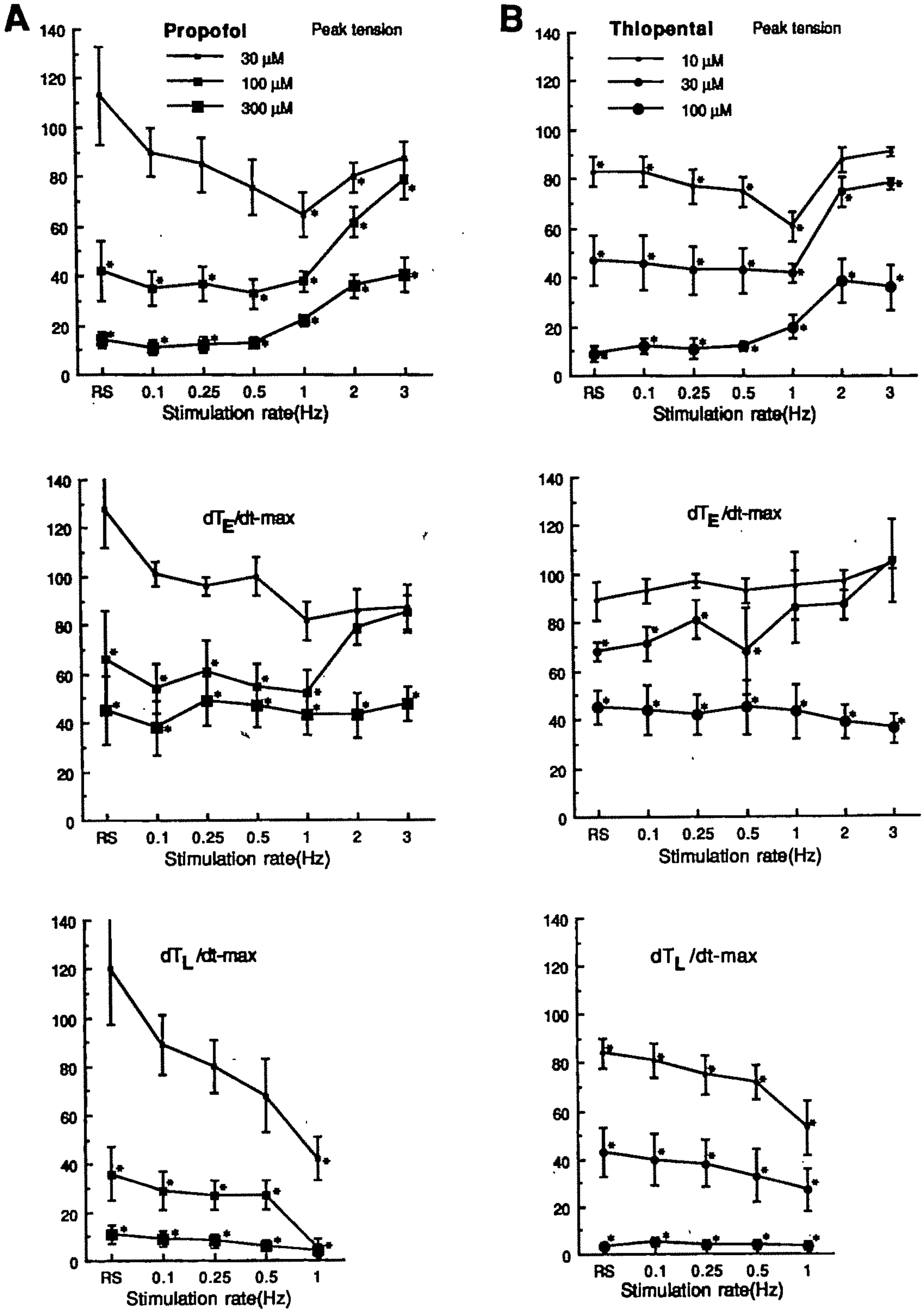

Figure 4. Effects of propofol and thiopental on myocardial contractions in 26 mM K^+ Tyrode's solution with 0.1 µM isoproterenol at various stimulation rates. Results are plotted as mean (±SEM) percent of control (n = 5–7). *Upper panels* show actions on peak tension. *Middle panels* show alteration in the maximum rate of early tension development (dT_E/dt max). *Lower panels* show alteration in maximum rate of late peaking tension (dT_L/dt max). *Difference ($P < 0.05$) from control. **A.** Effects of increasing concentrations of propofol (added as Intralipid emulsion). **B.** Effects of increasing concentrations of thiopental.

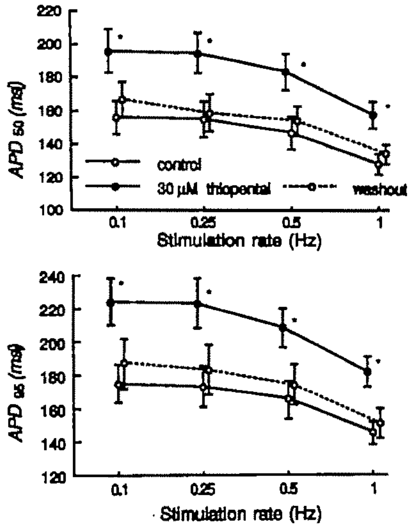

Figure 5. Effects of 30 μM thiopental on slow action potential duration at 50% repolarization (APD_{50}) or at 95% repolarization (APD_{95}). Results are plotted as mean ± SEM of measured values. *Difference ($P < 0.05$) from control and washout.

Table 3. Effects of Propofol and Thiopental on Contractions in Reduced (40 mM) Na^+ Tyrode's Solution

	Concentration (μM)	Peak tension (% control)		dT/dt max (% control)	
		0.01 Hz	0.1 Hz	0.01 Hz	0.1 Hz
Propofol	100	72 ± 9	76 ± 5	85 ± 6[a]	82 ± 8
	300	64 ± 7	62 ± 6	82 ± 4[a]	75 ± 10[a]
Thiopental	30	61 ± 9	78 ± 1	85 ± 5	86 ± 1[b]
	100	46 ± 5[c]	51 ± 5	54 ± 4[d]	63 ± 6[b]

Values represent mean ± SEM for four experiments.

[a] $P < 0.05$, difference from peak tension by paired t-test.

[b] $P < 0.01$, difference from peak tension by paired t-test.

[c] $P < 0.05$, difference between 100 μM propofol and 300 μM thiopental by unpaired t-test.

[d] $P < 0.01$, difference between 100 μM propofol and 300 μM thiopental by unpaired t-test.

rum of 93 μg/mL (352 μM) (35), whereas 12.6 μg/mL (48 μM) represents the average anesthetic plasma concentration (AD_{50}) (36). Assuming 83%–86% protein binding (35,36), the average anesthetic and peak concentrations of unbound thiopental achieved in humans should be about 1.9–16 μg/mL (7.2–60 μM). This calculated clinical range of free (non-protein-bound) thiopental is indicated in Figure 6. From Cockshott (37), the typical peak serum values for propofol may be as high as 8 μg/mL (44 μM), with infusions yielding values of 4–5 μg/mL (22 μM); its clinical range is also indicated in Figure 6. Comparing equally effective clinical concentrations of drug at the higher, near physiologic rates (≥3 Hz), it is apparent that the depressant action of thiopental on myocardial contractility (to 30%–60% of control) is greater than that of propofol (to 70%–80% of control).

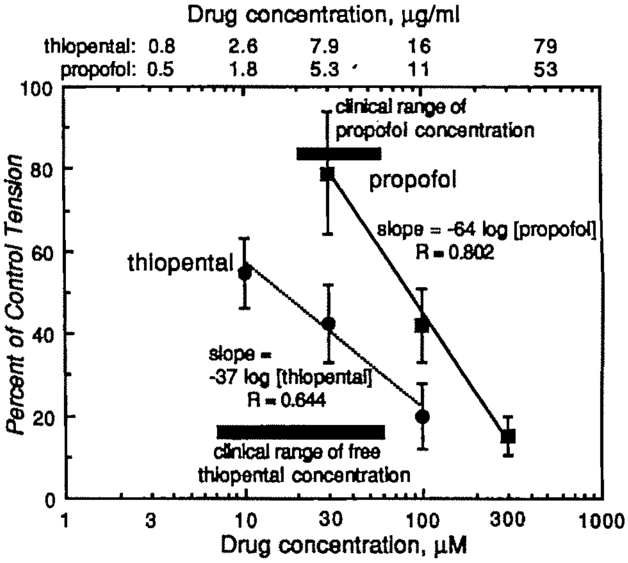

Figure 6. Concentration-response relation of thiopental and propofol. Myocardial peak tension observed at 3 Hz in normal Tyrode's solution is plotted as a percent of the control value. Drug concentrations on a log scale are indicated in μM (*lower scale*) and μg/mL (*upper scale*), as well as the clinical concentration ranges of propofol and of free (unbound to serum proteins) thiopental. The depression by 30 μM thiopental was greater ($P < 0.05$) than that by 30 μM propofol. The regression lines are shown for tension as a function of log [drug]. The slopes of the dose response (as a function of the log [drug]) and the correlation coefficient are indicated. The 90% confidence limits for the slope of the dose responses are −17 to −57 × log [thiopental] and −89 to −40 × log [propofol], indicating that the drugs did not differ significantly in the slope of the dose responses.

However, relating the total clinical serum concentrations of propofol to free aqueous drug concentrations in serum or perfusate is difficult. Assuming that the octanol/water partition of ~5000 approximates the partitioning between lipid and water in the commercial Intralipid preparation, then 0.15% of drug is in the aqueous phase with a concentration of ~0.1 mM, and the suspended lipid phase (11.2%) has a concentration of ~500 mM. When the appropriate volume of emulsion is added to superfusing solutions to obtain total concentrations of 30, 100, and 300 μM, the calculated aqueous concentrations are 22, 46, and 66 μM. (Calculated according to the equation: Aqueous drug concentration = Total quantity of drug ÷ {Solution volume × [1 + % Lipid × (Partition coefficient − 1)]}, where the percent lipid was calculated from the dilution of the Intralipid that contained the equivalent of 11.2% lipid [soybean lipid plus purified egg phosphatide].) Although the rate of exchange between the propofol-containing liposomes, the aqueous phase, and serum proteins is not reported, it is known that a very large fraction (98%) of propofol is bound to serum protein in blood (38), as expected for such a lipophilic compound. Therefore, the unbound estimated propofol superfusate concentrations of 22, 46, and 66 μM may be significantly higher than the concentration of unbound drug in serum. In the comparable clinical range, the effective propofol concentration may be lower than that achieved in this protein-free medium, and the difference in contractile depression between propofol and thiopental may be even greater than suggested by Figure 6.

The relatively modest effects of propofol on contractility at clinical concentrations do not explain the marked depression of systemic arterial blood pressure frequently observed experimentally (12,15) or clinically (3,4,6,7,13,16–18). However, the multiple studies that suggest that propofol decreases SVR (3,4,6,7,16,18) as well as causes venodilation (14,15,17) support the notion that the decrease in systemic arterial blood pressure that accompanies propofol administration is due primarily to relaxation of arteriolar and venous tone, combined with a modest effect of decreased myocardial contractility. Furthermore, the decreased SVR may in part compensate for myocardial depression, permitting maintenance of ventricular function and cardiac output under many circumstances (9,15,17).

The most characteristic electrophysiologic finding in this study was the consistent prolongation of the AP by thiopental, an effect previously observed by other investigators (33,39). Such delay of repolarization is consistent with a decrease in K^+ conductance, which has been substantiated by radioisotopic studies (33). Although an enhanced or prolonged inward current (Ca^{2+} or Na^+) could explain this phenomenon, such actions of thiopental seem unlikely in view of the suggestion that thiopental may depress Ca^{2+} influx. As previously reported in canine papillary muscle (39), we also found that 100 μM thiopental reduced dT/dt max, suggesting that thiopental inhibits the Ca channel mediated influx of Ca^{2+}. In addition, both pentobarbital and thiopental have been shown to reduce Ca^{2+} uptake in stimulated rat sympathetic ganglia, suggesting inhibition of voltage-gated Ca^{2+} influx (40). It has been postulated that in cardiac muscle the intracellular $[Ca^{2+}]$ has an important regulatory role on the AP duration. As the increase of intracellular Ca^{2+} after depolarizations may in part be responsible for activating a K^+ conductance and subsequent repolarization (41,42), depression of Ca^{2+} entry could contribute to AP prolongation. Alternatively, a direct depressant effect on the resting K^+ conductance could contribute to increased AP duration, as well as explain the observed slight depolarization of the resting potential and the spontaneously occurring APs in the partially depolarized preparations previously reported by Mantelli et al. (43). As dV/dt of APs actually measures net current, simultaneous decrease of inward and outward current may have counteracting effects. The failure to detect a decrease of the slow AP dV/dt max with 30 μM thiopental does not eliminate possible depression of Ca^{2+} currents by this lower dose if coincident depression of K^+ conductance was also occurring. Unlike the distinctive effects of thiopental, propofol had no effects on any AP characteristics. It is noteworthy that in a clinical study of electrocardiograms observed during propofol or thiopental administration, thiopental caused a significantly greater prolongation than propofol of the QT interval, the in vivo equivalent of cardiac AP duration (44).

Both propofol and thiopental selectively depressed the distinct late peaking tension observed with slow APs more than the early tension development characteristic of physiologic heart rates or observed in low-Na Tyrode's solution. Reiter et al. (45) have reported that this late peak tension is due to the Ca^{2+} that enters the cell during the initial phase AP, is taken up into the SR, and subsequently released late in depolarization. Procaine and other local anesthetics, isoflurane, and enflurane have been shown to selectively depress the late peak tension attributed to this late SR Ca^{2+} release (19,25,46). In contrast, ryanodine decreases the initial tension development (25) by putting the Ca release channel in a low conductance state and decreasing SR Ca^{2+} available for release (47,48). Although the source of activator Ca^{2+} for both the early tension development and the late-peaking tension is the SR, the specific Ca^{2+} pools are released via pharmacologically distinct mechanisms (25,46). Physiologic evidence for two types of cardiac SR Ca^{2+} release has also been recently presented (49). Thus these two intravenous general anesthetic agents have a pharmacologic feature in common with local anesthetics, and also isoflurane and enflurane, in selectively greater depression of the late SR Ca^{2+} release. In a contrasting study of thiopental on rabbit papillary muscle, Komai and Rusy (34) observed that 29–87 μM thiopental inhibited potentiated contractions significantly less than steady state contractions, suggesting that the capacity of SR to store and release Ca^{2+} is minimally affected by thiopental. The more modest depression of the early tension development by thiopental, both in normal and low-Na Tyrode's solution, is also consistent with a modest effect on the rapid initial Ca^{2+} release from the SR. Komai and Rusy suggest that the major action responsible for thiopental's negative effect is inhibition of transsarcolemmal Ca^{2+} influx. The lack of effect of propofol on slow AP dV/dt and the modest depression of dV/dt max by thiopental suggests that depression of Ca^{2+} entry may not totally account for the observed contractile depression. The depression of early tension development in reduced-Na^+ Tyrode's solution and at higher stimulation frequencies, in excess of apparent action on slow AP dV/dt, suggests that some effect of thiopental and propofol on the early SR Ca^{2+} release may contribute, although it is less prominent than the action on late tension.

In conclusion, propofol directly depresses the contractility of isolated ventricular myocardium; however, its depressant actions are more modest than those of thiopental at comparable clinical ranges. In contrast to propofol, thiopental altered the cardiac AP duration and slow AP more than did propofol, suggesting alteration of K^+ and Ca^{2+} fluxes.

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Operative Lung Constant Positive Airway Pressure With the Univent Bronchial Blocker Tube

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Constant positive airway pressure (CPAP) to the operative lung during one-lung ventilation (1-LV) with a double-lumen tube increases Pao_2; there have been no reports of application of CPAP to the operative lung during 1-LV with the Univent bronchial blocker (BB) tube. This study determined the method of administration and the effect on Pao_2 of 10 cm H_2O of CPAP to the operative lung during 1-LV (1-LV+10 CPAP) produced by the Univent BB system. We designed our CPAP system for the Univent BB using an in vitro lung model so that low O_2 flow rates (2–4 L/min) yielded clinically relevant levels of CPAP (5–20 cm H_2O) over a wide range of lung compliance. The CPAP system simply consisted of placing a resistance to a variable oxygen flow distal to the operative lung. Seven consenting patients who required thoracotomy and 1-LV were anesthetized and their tracheas were intubated with the Univent BB tube; the BB was inserted into the appropriate mainstem bronchus until the proximal surface of the BB cuff was just distal to the tracheal carina. Pao_2 was measured in the seven patients during 12 sequences of two-lung ventilation (2-LV), one-lung ventilation (1-LV), and 1-LV with 10 cm H_2O CPAP (1-LV+10 CPAP). 1-LV+10 CPAP was always instituted on the deflation phase of a previous single tidal inhalation. We found in our patients with a lung compliance of 32 ± 4 mL/cm H_2O that 2.4 ± 0.2 L/min of oxygen flow produced 1-LV + 10 CPAP. The mean ± SD Pao_2 during 2-LV, 1-LV, and 1-LV+10 CPAP was 347 ± 159, 127 ± 93, and 312 ± 122 mm Hg, respectively. The Pao_2 during 1-LV was significantly decreased compared with both 2-LV and 1-LV+10 CPAP (both $P < 0.001$), and there was no significant difference in Pao_2 during 2-LV compared with 1-LV+10 CPAP ($P > 0.2$). One-lung ventilation + 10 CPAP did not have any statistically significant hemodynamic effect or interfere with surgical exposure. We conclude that 1-LV+10 CPAP through the Univent BB tube is technically simple to administer and is potentially an efficacious treatment of hypoxemia during 1-LV.

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Operative exposure during thoracic surgery can be facilitated by one-lung ventilation (1-LV); however, the major risk of 1-LV is hypoxemia. Moderate levels of selective constant positive airway pressure (5–10 cm H_2O of CPAP) to the nonventilated operative lung using a double-lumen tube statically and slightly distends the operative lung, thereby decreasing the shunt through the operative lung and increasing Pao_2 to values close to those obtained during two-lung ventilation (2-LV) (1–10). Of course, CPAP to the operative lung must be applied on the deflation phase of a previous breath to achieve this oxygenation efficacy.

The Univent bronchial blocker (BB) tube (Fuji Systems Corporation, Tokyo, Japan) is a single-lumen tube that has a small channel on the anterior wall through which a cuffed hollow catheter (the BB) may be inserted into the mainstem bronchus of the operative lung to allow both 1-LV (BB cuff inflated) and 2-LV (BB cuff deflated) (11–14). Inserting the Univent BB system into the trachea and positioning the BB in the appropriate mainstem bronchus with a fiberoptic bronchoscope appears to be relatively easy compared to inserting and positioning a double-lumen tube, and the Univent tube does not have to be changed to a standard single-lumen tube at the end of a case if postoperative mechanical ventilation is required. However, the Univent BB system may be less versatile intraoperatively than a double-lumen tube because there have been no reports showing that application of CPAP to the nonventilated operative lung is clinically possible using the Univent system. This report shows that it is technically simple and clinically very efficacious to administer CPAP to the operative lung during 1-LV through the Univent BB tube.

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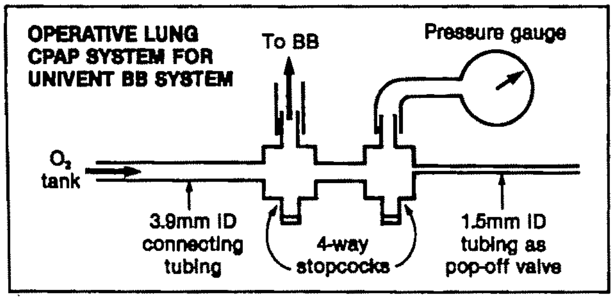
OPERATIVE LUNG CPAP SYSTEM FOR UNIVENT BB SYSTEM
To BB
Pressure gauge
O_2 tank
3.9mm ID connecting tubing
4-way stopcocks
1.5mm ID tubing as pop-off valve

Figure 1. The schematic shows the operative lung CPAP system for the Univent bronchial blocker (BB) used in this study. The CPAP was measured by a pressure gauge.

Methods

In Vitro Lung Model

We designed our CPAP system for the Univent BB using an in vitro lung model so that low O_2 flow rates would yield clinically relevant levels of CPAP. The model consisted of a variably compliant test lung (range 150–10 mL/cm H_2O) that had a known instantaneous volume. The test lung was connected to a 10-mm ID mainstem bronchus of polyvinylchloride tubing. The Univent BB was inserted into the mainstem bronchus and its cuff was inflated. The lumen of the BB was connected to the CPAP system shown in Figure 1. The length and internal diameter of the inlet tubing was 90 cm and 3.9 mm, respectively; the length and internal diameter of the pop-off tubing was 15 cm and 1.5 mm, respectively, and the length and the internal diameter of the tubing to the BB was 60 cm and 3.9 mm, respectively. These three tubes were connected by four-way stopcocks (Mallinkrodt No. 91046, Glen Falls, N.Y.). The ratio of the inlet to the pop-off tubing diameter of the CPAP system was 2.6. The CPAP system was connected to a standard E cylinder; the CPAP level was measured with a pressure manometer and was directly proportional to the O_2 flow rate.

In Vivo Patient Studies

Seven patients (age, 20–75 yr; weight, 50–90 kg; height, 150–190 cm), who were variously scheduled for thoracotomy for right upper lobectomy ($n = 2$), left lower lobectomy, left transthoracic T9-T10 vertebrectomy, left transthoracic T8-T9 corpectomy, drainage of right empyema, and left thoracic sympathectomy were studied after informed consent had been obtained. The patients were anesthetized with intravenous thiamylal (4 mg/kg), fentanyl (10–15 μg/kg initial bolus followed by a 2-$\mu g \cdot kg^{-1} \cdot h^{-1}$ continuous infusion), and isoflurane (0.5%–1.0% in balance O_2) and paralyzed with a nondepolarizing relaxant. The Univent BB tube was positioned under direct vision with a fiberoptic bronchoscope so that the proximal surface of the BB cuff was a few (1–5) millimeters distal to the tracheal carina. Depth of insertion of the BB in this position with respect to the upper gum line was noted. Two-lung ventilation tidal volume was 12 mL/kg, and respiratory rate was adjusted so that $Paco_2 = 37 \pm 6$ mm Hg. One-lung ventilation (tidal volume was 10 mL/kg and respiratory rate increased approximately 30% so that $P\textsc{et}co_2$ did not change by more than 5 mm Hg in the first 20 min of 1-LV. Two-lung ventilation static compliance was calculated by dividing tidal volume by plateau inspiratory pressure. One-lung ventilation with 10 cm H_2O CPAP (1-LV + 10 CPAP) with the pressure referenced to the external pressure manometer) was initiated (with the device developed in the in vitro model) during the deflation phase of an immediately preceding single tidal volume. The single tidal volume was delivered by one 50-psi jet ventilation to the BB lumen, and the operative lung within the open hemithorax during this inhalation was directly observed to expand to a degree that the surgical conditions permitted. The oxygen flow rate required to produce 10 cm H_2O CPAP was noted. Data during 1-LV and 1-LV + 10 CPAP were obtained when the lung was retracted for surgical exposure and there was no surgical interference with the operative lung blood vessels (handling, ligation, snare).

The experimental sequence consisted of measuring arterial blood gases, peak inspiratory pressure, blood pressure, and heart rate after each 20-min sequential period of 2-LV, 1-LV, and 1-LV + 10 CPAP. The first experimental period was always 2-LV, the second 1-LV, and third 1-LV + 10 CPAP; if time and lack of surgical interference with operative lung blood vessels permitted (five patients), the data were collected in the reverse order, namely another (the fourth) period of 1-LV, a fifth of 1-LV + 10 CPAP, and a sixth of 2-LV. Twelve complete 2-LV, 1-LV, 1-LV + 10 CPAP sequences were obtained in the seven patients.

Data were analyzed by analysis of variance and paired *t*-test with Bonferroni correction (level of significance was $P < 0.05$) and are presented as individual patient data and as mean ± standard deviation (SD).

Results

The in vitro lung model O_2 flow-CPAP relationship is shown in Figure 2. For a lung compliance of 150 mL/cm H_2O, O_2 flow rates of 1.6–3.3 L/min produced CPAP of 5–20 cm H_2O, respectively, and for a lung compliance of 10 mL/cm H_2O, O_2 flow rates of 2.0–4.1 L/min produced CPAP of 5–20 cm H_2O, respectively. An O_2 flow of 2.4 ± 0.2 L/min was

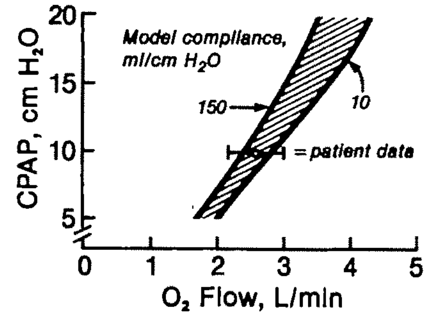

Figure 2. The oxygen flow rates required to produce various levels of CPAP in the in vitro test lung, which had a compliance ranging from 10 to 150 mL/cm H_2O. All of the in vitro test lung data are within the shaded band. The in vivo patient 1-LV + 10 CPAP O_2 flow of 2.4 ± 0.2 L/min for the seven patients in the study with a 2-LV compliance of 32 ± 4 mL/cm H_2O lies well within the in vitro band of data.

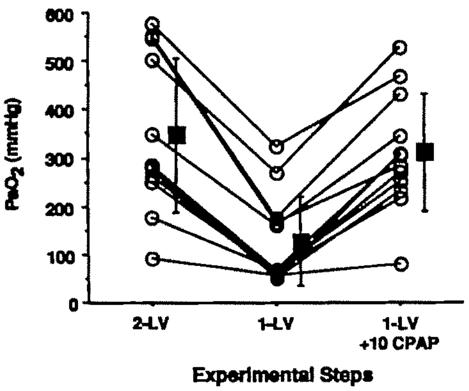

Figure 3. Pa_{O_2} values for the 12 individual experimental sequences of two-lung ventilation (2-LV), one-lung ventilation (1-LV), and one-lung ventilation with 10 cm H_2O CPAP (1-LV + 10 CPAP). The mean ± SD Pa_{O_2} value for each of the three experimental sequence steps (2-LV, 1-LV, 1-LV + 10 CPAP) is offset to the right of the individual data points. Pa_{O_2} during 1-LV was significantly less ($P <$ 0.001) than during both 2-LV and 1-LV + 10 CPAP, but Pa_{O_2} during 2-LV was not significantly different from 1-LV + 10 CPAP.

required to produce 1-LV + 10 CPAP in our patients with a 2-LV compliance of 32 ± 4 mL/cm H_2O; this O_2 flow rate was well predicted by the in vitro model.

Figure 3 shows the mean ± SD and individual sequence Pa_{O_2} results during 2-LV, 1-LV, and 1-LV + 10 CPAP (12 complete sequences in seven patients). Pa_{O_2} during 1-LV was significantly decreased compared with both 2-LV and 1-LV + 10 CPAP (both $P <$ 0.001), and there was no significant difference in Pa_{O_2} during 2-LV compared with 1-LV + 10 CPAP ($P >$ 0.2). Unfortunately, 1-LV + 10 CPAP was least effective in the patient with the lowest 1-LV Pa_{O_2}. Pa_{CO_2} during 2-LV was 37 ± 6 mm Hg, which was significantly less than the 42 ± 7 mm Hg and 41 ± 6 mm Hg during 1-LV and 1-LV + 10 CPAP, respectively ($P <$ 0.03); however, the Pa_{CO_2} during 1-LV compared with 1-LV + 10 CPAP were not significantly different.

There were no significant differences in blood pressure and heart rate between 2-LV, 1-LV, and 1-LV + 10 CPAP. In the five patients in whom two complete sequences could be obtained, there was no difference between the initial and the repeated sequence with respect to any given physiologic variable. The depth of insertion of the Univent BB was 29 ± 1 cm. One-lung ventilation + 10 CPAP did not interfere with surgical exposure in five patients, caused slight interference in one patient, and moderate interference in one patient.

Discussion

We found that applying 10 cm H_2O CPAP (with reference to our external pressure manometer) to the operative lung during 1-LV markedly increased Pa_{O_2}; the increase in Pa_{O_2} was nearly identical to that reported with the use of a double-lumen tube (1–10). We were able to administer CPAP to the operative lung through the lumen of the Univent BB by using the same principle of application of operative lung CPAP as with a double-lumen tube, namely, that of placing a resistance to a variable oxygen flow distal to the operative lung. We found that oxygen flow rates between 2 and 4 L/min through the pop-off tubing produced all clinically relevant levels of operative lung CPAP. However, the actual alveolar pressure produced by this system may be slightly lower than the pressure measured by our gauge because of the resistance of the BB tubing. Of course, if one or both of the stopcocks or the outlet tubing were partially and inadvertently occluded, the CPAP level could be much higher than desired and the pressure measured by the gauge might be considerably lower than that delivered to the lung. As the oxygen flow rate and outlet tubing resistance are the primary determinants of the level of operative lung CPAP, it is not surprising that we found that alteration in lung compliance in the in vitro lung model from 10 to 150 mL/cm H_2O had little effect on the level of CPAP produced.

The mechanism of oxygenation efficacy depends on the amount of CPAP applied. In dogs in the lateral decubitus position, it has been shown that low levels of CPAP (5–10 cm H_2O) to the nonventilated nondependent lung greatly increases Pa_{O_2} and decreases shunt, while blood flow to the nonventilated lung remains constant (1). Presumably, these levels of CPAP do not compress the small intraalveolar vessels in the nondependent lung. Thus, it is not surprising that we found, as have others (3), that the institution of 10 cm H_2O nondependent lung CPAP has no significant hemodynamic effect. Thus, low levels of CPAP simply maintain the patency of nondependent lung airways, allowing some oxygen distention of the gas-exchanging alveolar space in the nondependent lung without significantly affecting the pulmonary vasculature.

On the other hand, in the same dog study (1), 15 cm H_2O nondependent lung CPAP caused changes in Pa_{O_2} and shunt similar to those of 5–10 cm H_2O nondependent lung CPAP, while blood flow to the nonventilated nondependent lung decreased significantly. Therefore, high levels of nonventilated lung CPAP improve oxygenation by permitting oxygen uptake in the nonventilated lung as well as by causing blood flow diversion to the ventilated lung where oxygen and carbon dioxide exchange can take place. As low levels of nonventilated lung CPAP are as efficacious as high levels of nonventilated lung CPAP and have less surgical interference and hemodynamic implications, it is logical to first use low levels of nonventilated lung CPAP.

We found that when tidal volume was decreased from 12 to 10 mL/kg and respiratory rate was initially increased by 30% in changing from 2-LV to 1-LV, there was a small but statistically significant 5 mm Hg increase in Pa_{CO_2}. It seems reasonable to postulate that if tidal volume is decreased by 18% in changing from 2-LV to 1-LV, an increase in respiratory rate of 35%–40% will result in a nearly constant Pa_{CO_2}.

We found that when the cephalad surface of the BB was situated just below the tracheal carina, the depth of insertion was 29 ± 1 cm (to the upper gum line). This is in excellent agreement with a large study that examined the depth of insertion of double-lumen tubes where the end point for insertion for the double-lumen tube was when the cephalad surface of endobronchial cuff was just below the tracheal carina (15). This position is important for both the double-lumen tube and the Univent BB because it means that when CPAP is applied to the operative lung (the blocked lung), the CPAP will probably be applied to all of the operative lung (including the upper lobe). The fact that Pa_{O_2} during 1-LV + 10 CPAP was nearly equal to the Pa_{O_2} during 2-LV implies that we were able to distend the upper lobes of the blocked lung with the operative lung CPAP.

In comparison with a double-lumen tube, the Univent BB has several advantages and disadvantages. The advantages include easier insertion and positioning, no need for changing the tube to a single-lumen tube if postoperative mechanical ventilation is needed, and as with a double-lumen tube, hypoxemia during 1-LV can be treated with operative lung CPAP. With respect to ease of insertion, this is equivalent to a standard single-lumen tube and with respect to ease of positioning, it is easy to maintain ventilation around a bronchoscope while the right and left mainstem bronchi are identified and the BB is observed to enter the appropriate mainstem bronchus. The other two advantages are self-explanatory.

The disadvantages consist of very slow inflation and deflation of the operative lung through the small BB lumen, relatively easy blockage of BB lumen by fluids (secretions, pus, blood) from the operative lung making CPAP ineffective/unpredictable, the need to inflate the BB cuff with a relatively large seal volume of air (usually 4–7 mL) that is much greater than the volume of air required to distend the cuff to its natural shape (2–3 mL), and the very large outside diameter of the Univent BB tube (for internal diameters of 7.0, 8.0, and 9.0 mm the external diameters are 10.5, 11.5, and 12.5 mm, respectively). With respect to inflation of the lung, jet ventilation with a 50-psi source is very effective and quick, but it is absolutely mandatory that the anesthesiologist use a very short inspiratory time (0.5 s or less) and directly observe the expansion of the ventilated lung because with the chest wall open the lung inflates extremely quickly and the lung can easily be overdistended and traumatized. The relatively large volume of air required to obtain a BB cuff seal may cause the cuff to make contact with the bronchial wall over a very small surface area and with very high pressure. As the area of contact is probably small, the Univent BB may be susceptible to leaking, especially when the mainstem bronchus is distorted by surgical manipulation, and to backing out, especially when distal traction is exerted on the tracheobronchial tree (16). The remaining two disadvantages are self-explanatory.

We have shown that it is technically simple and clinically very efficacious to apply CPAP to the operative lung with a Univent BB tube. Thus, with operative lung CPAP capability, the versatility of the Univent BB tube is increased toward that of a double-lumen tube. As the Univent BB tube may be easier to insert and correctly position compared to a double-lumen tube and the hypoxemia produced by 1-LV can be effectively treated with operative lung CPAP, the Univent BB tube may be used with greater frequency and confidence in the future.

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Force Applied During Tracheal Intubation

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This study quantitated the force applied during tracheal intubation to determine (a) whether the force differed among novice and experienced intubators, and (b) whether the force required differed when intubating patients' tracheas versus intubating the trachea of a commonly used training mannequin. We studied 27 tracheal intubations performed by 17 experienced (>100 prior intubations) and 10 novice (<10 prior intubations) intubators. Each intubation was performed with a No. 3 Macintosh blade instrumented with strain gauges to determine force applied in the sagittal plane. The mean force applied was 24.6 ± 2.9 N (mean ± SEM) and the maximum force applied by each intubator was 47.6 ± 3.8 N. There was no difference between groups in the mean force applied (28.8 ± 6.1 N for the novice group vs 22.3 ± 2.7 N for the experienced group, $P = 0.27$) nor in the maximum force applied (55.1 ± 6.5 N for the novice group vs 43.2 ± 4.7 N for the experienced group, $P = 0.08$). The only difference was in the impulse (force × duration), which was more for the novice group largely because of the longer average duration of intubation (40 ± 12 s vs 19 ± 4 s, $P = 0.06$). Among experienced intubators, we found that applied force correlated with patient weight and Mallampati class. Intubation of the Laerdal Airway Management Trainer required mean forces comparable to those required in patients (26.6 ± 2.5 N vs 22.3 ± 2.9 N), although the maximum force applied during the intubation effort was greater (58.3 ± 4.7 N vs 43.2 ± 4.7 N, $P < 0.05$). We conclude that force applied during intubation of the trachea is easily quantified but is not clearly different between novice and experienced operators. However, a device such as we used can distinguish excessive or inadequate force. We also suggest that future airway models may need to be modified to reflect the forces actually required in patients.

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The force applied during tracheal intubation has not been quantitated. Such data might be useful in training, in design of intubation models, and in assessing the potential for injury after intubation (1).

Beginners often struggle with a laryngoscopy, at times expending great effort and at other times using inadequate force. We believed that biomechanical analysis of the force applied during tracheal intubation could lead to better feedback during teaching. Furthermore, we believed that analysis of the applied force could be used to create specifications for an intubation mannequin. The study reported here examined the force applied to the oropharyngeal tissues by the laryngoscope blade during intubation of the trachea.

Methods

We studied a total of 27 tracheal intubations in patients, performed by 17 experienced (>100 prior intubations) and 10 novice (<10 previous intubations) staff members. Experienced intubators included anesthesiology attending staff, senior residents, and nurse anesthetists. Inexperienced intubators included paramedic students ($n = 4$), medical students ($n = 3$), and residents specializing in fields other than anesthesiology ($n = 3$).

This study was approved by the Human Subjects Review Board of the University of Washington, and all patients consented in writing to participate. Each patient was examined by one of the authors, and a classification of the airway was noted according to the model of Mallampati et al. (2). Only intubations done after the intravenous administration of a muscle relaxant were studied. The operators were instructed to follow their normal procedures (or, in the case of novices, the procedures advised by their trainer).

We used a No. 3 Macintosh laryngoscope blade and handle (Penlon Ltd.) instrumented with strain gauges (CEA-13-125UW-120, Micromeasurements, Raleigh, N.C.). The strain gauges were located on the top and bottom surfaces of the end of the blade 3 cm from the handle. This arrangement permitted the sensing of bending of the blade, due to a force acting

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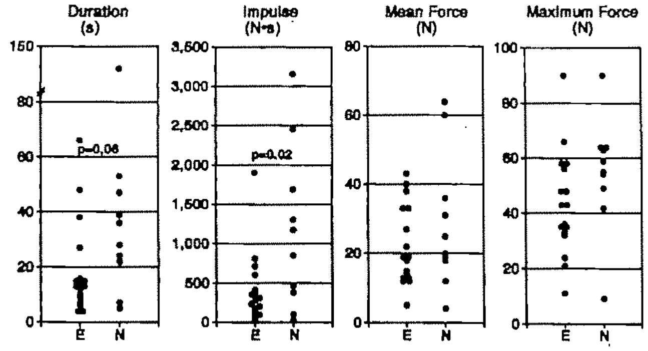

Figure 1. Comparisons of duration, impulse, and mean and maximum force for novice versus experienced intubators. The units are seconds for duration, newtons × seconds for impulse, and newtons for mean and maximum force. E and N denote experienced versus novice intubators. Each point represents one intubation.

at the tip creating a cantilever moment. The instrument measures the magnitude of the force in the sagittal plane but does not measure the angle of the vector. The gauges were configured in a half-Wheatstone bridge to be self-temperature compensating. The signal was amplified (model 2301 Micromeasurements) and recorded at 50 Hz using an analog-to-digital convertor and a microcomputer. Recording began when force was first applied to the blade of the laryngoscope and ended when a stable baseline was again reached as the instrument was removed from the mouth.

Data analysis included noting the duration of the intubation attempt, the maximum force achieved, the mean force used, and the impulse defined as the integral of the force over the time interval during which the force acts. Eleven of the experienced operators also intubated a mannequin (Laerdal Airway Management Trainer) and the same data observations were performed. Data are reported as mean ± SEM. Data were analyzed using Student's *t*-test for unpaired data and the Pearson correlation coefficient. We excluded from analysis intubations that resulted in force being applied to the upper teeth (the lower side of the blade) as this resulted in compression of the strain gauges and invalid readings. Force is expressed in newtons (N) ($1 \text{ N} = 1 \text{ kg·m·s}^{-2}$).

Results

The mean applied force during tracheal intubation was 24.6 ± 2.9 N, with an average maximum of 47.6 ± 3.8 N. The novice group did not differ from the experienced group in either mean force or maximum force applied (Figure 1) (mean of 28.8 ± 6.1 N for the novice group vs 22.3 ± 2.7 N for the experienced group, $P = 0.27$ and maximum of 55.1 ± 6.5 N for the novice group vs 43.2 ± 4.7 N for the experienced group, $P = 0.08$). The impulse was significantly more for the novice group, but this was largely accounted for by a longer average duration of intubation (40 ± 12 s vs 19 ± 4 s, $P = 0.06$).

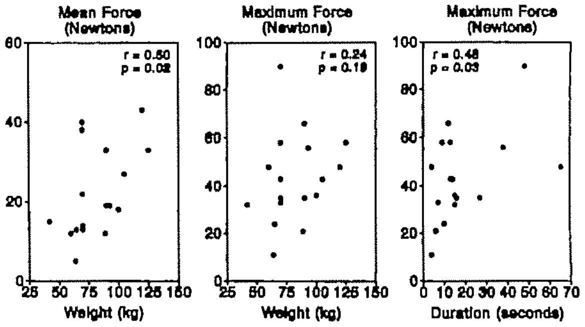

Figure 2. Mean and maximum force as a function of weight and maximum force as a function of duration. Graphs are for experienced intubators only. Each point represents one intubation.

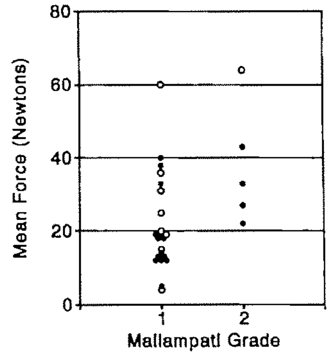

Figure 3. Mean force applied by intubators as a function of Mallampati grade. Each point represents one intubation. *Closed circles* represent experienced intubators and *open circles* represent novice intubators.

We found that mean but not maximum applied force correlated with patient weight among the experienced group (Figure 2). Maximum force correlated only with the duration of intubation (Figure 2). There was a trend toward a negative correlation of age with maximum force required ($r = -0.32$, $P = 0.07$). A 38% greater force was required in patients of Mallampati class 2 compared with Mallampati class 1 ($P < 0.05$) (Figure 3).

Intubation of the mannequin's trachea by experienced intubators resulted in a maximum force of 58.3 ± 4.7 N for the mannequin vs 43.2 ± 4.7 N for the patients ($P < 0.05$) (Figure 4). Mean force, however, did not differ (26.6 ± 2.5 N vs 22.3 ± 2.9 N).

Discussion

Measurements of force applied during laryngoscopy have not been described. A previous account of such a device (3) stated that the measurements of force had

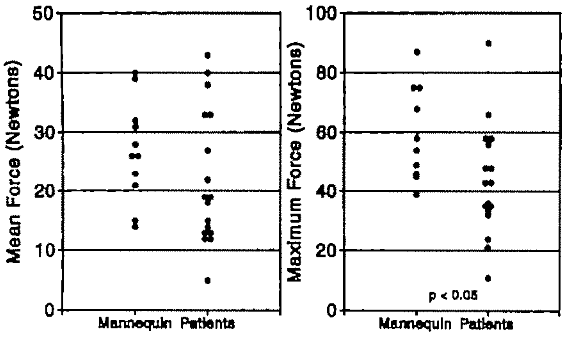

Figure 4. Comparison of mean and maximum force applied by experienced intubators in mannequins and in patients. Each point represents one intubation.

been instructive to trainees. However, that report described the device but did not include any data, and no further experience has been published. An abstract published in 1982 noted that a "pressure" of 4 kg has been measured (4). No complete report could be found of that study. Kilograms are actually a measure of mass, but we can assume this represents a force of 39 N, comparable to the forces we measured. (Force = mass × acceleration. Acceleration = gravity = 9.8 $\mathrm{m \cdot s^{-2}}$. Thus, 4 kg × 9.8 $\mathrm{m \cdot s^{-2}}$ = 39 $\mathrm{kg \cdot m \cdot s^{-2}}$ = 39 N.)

Based on the data obtained, the force applied along the sagittal axis by the blade of a laryngoscope by trainees was generally in the same range as that of experienced clinicians. However, in two cases (Figure 1) mean force by novice intubators was more than two standard deviations above the mean for experienced intubators. Force measurements might be useful in providing immediate feedback to trainees in such cases as an indication that other factors such as head position or force vector might need modification. We also noted that several novice intubators initially applied no measurable force. This does not appear in the data as their supervisors then encouraged the use of more force to accomplish the intubation, but direct feedback could also have been of value in these cases.

Had we studied a larger number of intubations, it is possible that the trends toward greater maximum and mean force by the novice group might have become statistically significant. However, because of the large overlap between the novice and experienced groups, applied force was not a clear distinguishing variable between the two groups. The major value of an instrumented laryngoscope would thus be in identifying outliers.

The limiting factor in force applied may well be the weight of the head. Head weight averages 7% of body weight, or approximately 50 N in a 70-kg (686 N) person (5). Assuming a relatively flexible cervical spine, the maximum force that could be applied vertically would be equal to the weight of the head.

Among the experienced intubators, we found that patient weight correlated significantly with the force applied. However, the correlation coefficient of 0.50 demonstrated that the force used is multifactorial. This correlation may in part be due to increased head weight as body weight increases but might also be due to the need to compress soft tissues.

We also found that patients of Mallampati class 2, signifying a 0.66 probability of a "difficult airway" (2), required a 38% higher average force. However, in this study the Mallampati class was highly correlated with weight and thus may not provide an independent predictor of force required.

The trend toward less force required with advancing age was independent of weight and may be attributable to greater laxity of muscle and tendons with advancing age.

Intubation of the widely used Laerdal mannequin trainer required a greater maximum but not mean force. This may reflect the characteristics of the plastic used for the mannequin's tongue. The stiff plastic required a greater force to deform it initially and move it out of the way during intubation but no greater force to hold it out of the way. The greater maximum force used was reflected in the subjective comments of the intubators that the mannequin was more difficult to intubate than is the average patient. Thus, a more pliable plastic might better approximate the actual feel of a patient.

Our data describe the scalar magnitude but not the direction of the force. The magnitude of force is just one of the components of tracheal intubation, along with head positioning and force vector direction. During instruction, head positioning and direction of force are observable to a trainer, whereas magnitude is not. An instrumented laryngoscope could provide the trainer and the trainee with more information to improve performance. Based on our data, this would be useful in the fraction of attempted intubations where the applied force deviates markedly from the norm. Our findings provide further support for the use of the Mallampati classification and/or weight in predicting intubation difficulty, as the classification was predictive of intubations requiring greater effort. We were surprised to find that the measurements in the mannequin did not differ more from those in the patients, given many subjective comments on the differences in "feel." It is possible that much of the subjective difference is attributable to the greater maximum force required, raising the possibility that improved materials might improve simulation.

We conclude that the instrumented laryngoscope we describe can be used to identify applied force during intubation, but that applied force is not a major distinguishing characteristic among novice operators. We also conclude that substantially greater force is required to intubate the airway mannequin than is required for the average patient.

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Accuracy of the FEF CO_2 Detector in the Assessment of Endotracheal Tube Placement

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The sensitivity and reliability of the FEF end-tidal CO_2 detector were investigated for its suitability in the assessment of correct placement of an endotracheal tube. Sensitivity was determined by having eight blinded volunteers observe the color change in the FEF detector with the administration of different volumes and varying CO_2 concentrations of gas mixture. The color change in the FEF detector was also assessed during esophageal ventilations before and after administration of carbonated beverage into the stomach of swine and during cardiopulmonary resuscitation in swine. An interpersonal variation was present among the blinded observers during the color-matching process. Different colors were observed with the same volume and CO_2 concentration of gas mixture. During esophageal ventilations before or after the administration of carbonated beverage, the FEF detector was neither accurate nor rapid in identifying esophageal placement of the endotracheal tube. The "C" color was displayed during the initial six ventilations in one swine, and esophageal intubation would have been missed. The FEF detector could (by displaying a "C" color) identify one of six correctly intubated swine during cardiopulmonary resuscitation. In conclusion, the FEF CO_2 detector does not have the characteristics to reliably assess the correct placement of an endotracheal tube.

(Anesth Analg 1992;74:415–9)

Unidentified esophageal intubation remains a major cause of avoidable morbidity and mortality in anesthesia (1,2). Of the available methods of detecting esophageal intubation, the presence of carbon dioxide (CO_2) in the expired gas is probably the most convenient and reliable (3). One drawback of capnography is that it requires electronic equipment like the infrared monitor or the mass spectrometer to measure and display the waveform of CO_2 present in the expired gas. This problem may be overcome by using the newly introduced FEF CO_2 detector (Fenem, New York, N.Y.), a small disposable device totally devoid of electronics. It has a nontoxic chemical indicator strip that responds quickly to exhaled CO_2 by a reversible color change in a semiquantitative fashion when placed between the endotracheal tube and a breathing circuit. The color change is divided into three ranges: purple hue color is in the "A" range and represents 0.03% to <0.5% end-tidal CO_2. The "B" range is a continuance of tan hues representing 0.5% to <2% end-tidal CO_2, and the "C" range is a range of yellow hues that represents the approximately 2% to 5% end-tidal CO_2.

The performance of any device is best verified with conditions simulating the worst scenario during which it might be used. Satisfactory performance under those conditions will establish the reliability and dependability of the device in everyday practice. Although the reliability of the FEF CO_2 detector has been investigated under normal circumstances, its performance under adverse conditions has not yet been determined (4–7). The two clinical situations during which a capnometer may have difficulty assessing correct endotracheal tube placement are those of cardiopulmonary resuscitation (CPR) and accidental esophageal intubation after ingestion of carbonated beverages (8,9).

The purpose of this study was to determine (a) the sensitivity of the FEF detector and (b) its accuracy in assessing correct placement of the endotracheal tube during cardiopulmonary resuscitation and esophageal intubation after ingestion of a carbonated beverage.

Methods

Five concentrations (0.5%–2.5%) of CO_2 in oxygen were mixed in a 20-L Douglas bag. The precalibrated Beckman LB II infrared CO_2 monitor was connected to the Douglas bag to check the CO_2 concentration. Using a combination of syringes, volumes of 40–1000 mL of the five concentrations of CO_2 were injected in 1–2 s

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through the FEF detector in a random fashion with a new detector used for each CO_2 concentration. Eight volunteers (with no history of color blindness and no prior training), blinded to the concentration of CO_2 and volume of gas injected, were asked to match the color change of the indicator with the color chart provided by the manufacturer. After every color match, the FEF detector was flushed with 1.0 L of atmospheric air to restore the original color.

With approval of the institutional animal investigation committee, anesthesia was induced in six Yorkshire swine with ketamine (15–20 mg/kg IM). After loss of consciousness, anesthesia was maintained with pentobarbital (20 $mg \cdot kg^{-1} \cdot h^{-1}$ IV) and a 7.0-mm endotracheal tube was placed through a tracheostomy. The animals were mechanically ventilated with a gas mixture of 30% oxygen in nitrogen and a tidal volume of 15 mL/kg at a rate to maintain normocarbia.

Monitors were placed to record the following: continuous electrocardiogram, mean systemic arterial pressure via a catheter in the carotid artery, end-expired CO_2 from the sample port attached to the endotracheal tube connector (Beckman LB II), and the color of the FEF CO_2 detector placed between the endotracheal tube and the breathing circuit. After recording the end-expired CO_2 and the color obtained with the FEF CO_2 detector during tracheal ventilation, the ventilator was switched to another 7.0-mm endotracheal tube placed in the esophagus through the mouth. End-expired CO_2 levels and FEF detector color changes were again recorded with six esophageal ventilations. The ventilator was reconnected to the tracheal tube, and the stomach was suctioned with a gastric tube passed through the esophageal tube. One hundred fifty milliliters of carbonated beverage (Diet Coke, Coca-Cola Bottling Company) at 2°C was then administered into the stomach through the gastric tube. Six more esophageal ventilations were administered after removal of the gastric tube, and end-expired CO_2 levels and FEF detector color change were recorded. The stomach was again suctioned, and the esophageal tube was removed.

Ventricular fibrillation was induced with 20 mL of concentrated KCl IV, and chest compression was started at a rate of 70–80 compressions per minute with the same setting on the ventilator. In swine 6, CPR was started 15 min after the onset of ventricular fibrillation. Adequacy of CPR was assessed by maintaining a minimum mean arterial pressure in the range of 30–35 mm Hg. End-expired CO_2 and color change in the FEF CO_2 detector were recorded continuously before and during CPR.

Statistical analysis was performed using a logistic regression. This model examines the relation between the color range observed and CO_2 concentration and volume (log volume was used for analysis). $P < 0.05$ was considered statistically significant.

Results

The color-matching process was not straightforward. The problem encountered was that the FEF detector color after injection of gas did not precisely match the A, B, or C color chart. When this occurred the observers selected from the chart whatever they thought was closest to the FEF detector color. An interpersonal variation was evident throughout the color-matching process. There was a difference in color range observed among the observers for the same volume and CO_2 concentration of gas mixture across the whole spectrum of volumes and CO_2 concentrations.

With a CO_2 concentration between 0.5% and 1.5%, the observers matched the A, B, and C color range with a frequency of 10%, 74%, and 16%, respectively (Table 1). The proportion of color-matched A, B, and C changed to 0%, 36%, and 64% with CO_2 concentration between 2.0% and 2.5%.

The color of FEF detector was influenced by volume and CO_2 concentration of gas injected (Table 1). The following results were reached using a logistic regression analysis. For a given CO_2 concentration, the observers chose a lower color range (A over B and C or A and B over C) 8.38 times more frequently at a low volume than at a volume 1 log volume higher ($P < 0.0001$). A lower color range was selected 22.46 times more often at a low CO_2 concentration than at a CO_2 concentration 1% higher ($P < 0.0001$). There was no significant interaction between volume and CO_2 concentration ($P = 0.4916$).

End-expired CO_2 concentrations and the FEF indicator color did not follow any definite pattern with the six esophageal ventilations, either before or after the administration of carbonated beverage, and they remained constant during all six tracheal ventilations both before and during CPR (Table 2). The mean CO_2 concentrations observed with esophageal ventilation before and after the administration of carbonated beverage were 0.3% ± 0.2% (mean ± SD) and 1.3% ± 1.5%, respectively. Before ventricular fibrillation, CO_2 concentrations of 4.9% ± 0.9%, which decreased to 1.1% ± 0.6% during CPR, were obtained with tracheal ventilations.

With esophageal ventilations (Table 2), the A color range (CO_2 range of 0%–0.7%) was observed in swine 1, 3, 4, and 6. In swine 1, 3, and 6, it changed to B after the third ventilation without a significant increase in end-expired CO_2 concentration. Esophageal ventilations produced a B color range in swine 2

Table 1. Variation in Color Selection Among Eight Volunteers With the FEF End-Tidal CO_2 Detector at Different Volumes and Concentrations of CO_2

	CO_2														
	0.5%			1.0%			1.5%			2.0%			2.5%		
Volume (mL)	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
40	7	1	0	4	4	0	0	8	0	1	5	2	0	6	2
50	3	5	0	0	8	0	0	6	2	0	5	3	0	0	8
75	2	6	0	0	8	0	0	7	1	0	5	3	0	3	5
100	5	3	0	0	8	0	0	8	0	0	6	2	0	4	4
125	1	7	0	0	8	0	0	7	1	0	5	3	0	1	7
150	1	7	0	0	7	1	0	6	2	0	4	4	0	0	8
175	6	2	0	1	7	0	0	8	0	0	7	1	0	8	0
200	2	6	0	0	8	0	0	4	4	0	4	4	0	0	8
300	0	8	0	0	8	0	0	3	5	0	3	5	0	0	8
400	2	6	0	1	7	0	0	8	0	0	7	1	0	5	3
500	0	8	0	0	7	1	0	2	6	0	3	5	0	0	8
600	1	7	0	0	7	1	0	2	6	0	3	5	0	0	8
700	0	8	0	0	8	0	0	3	5	0	3	5	0	0	8
800	2	6	0	0	8	0	0	4	4	0	3	5	0	1	7
900	0	8	0	0	8	0	0	3	5	0	1	7	0	0	8
1000	0	8	0	0	7	1	0	3	5	0	2	6	0	0	8

A, B, C, color ranges.

Table 2. End-Tidal CO_2 Level and Color of FEF End-Tidal CO_2 Detector Observed With Esophageal Ventilation Before and After Administration of Carbonated Beverage (Diet Coke, Coca Cola Bottling Co.) and With Tracheal Ventilation Before and During Cardiopulmonary Resuscitation

		Esophageal				Tracheal			
		Before Coke		With Coke		Before CPR		CPR	
Swine	Ventilation	ET CO_2 (%)	Color range	ET CO_2 (%)	Color range	ET CO_2 (%)	Color range	ET CO_2 (%)	Color range
1	1st	0.3	A	0	A	4.3	C	1.0	B
	3rd	0.7	A	0.1	B	4.2	C	1.3	B
	6th	0.3	B	1.0	C	4.2	C	1.3	B
2	1st	0.5	B	5.3	C	5.8	B	1.7	C
	3rd	0.4	B	4.0	C	5.7	C	1.8	C
	6th	0.3	B	3.4	C	5.7	C	1.8	C
3	1st	0.3	A	0.1	A	4.4	B	0.5	B
	3rd	0.2	A	0.3	B	4.5	C	0.5	B
	6th	0.1	B	0.1	B	4.5	C	0.5	B
4	1st	0	A	0	A	4.2	C	1.3	B
	3rd	0	A	0	A	4.3	C	1.3	B
	6th	0	A	0	A	4.3	C	1.3	B
5	1st	0.8	C	1.9	C	4.1	C	1.3	B
	3rd	0.6	B	1.2	C	4.1	C	1.1	B
	6th	0.3	B	0.8	B	4.1	C	1.1	B
6	1st	0.1	A	2.5	B	6.2	C	0	A
	3rd	0.3	A	2.0	C	6.3	C	0	A
	6th	0.2	B	1.8	C	6.5	C	0	A

during all six breaths and a C color range, which changed to B after the second ventilation, in swine 5.

The color range observed with esophageal ventilation was A in swine 1, 3, and 4 (CO_2 range of 0%–1.2%), after the administration of 150 mL of carbonated beverage, and it changed to B and C in swine 1 and 3 during the following ventilations (Table 2). A C color was initially observed in swine 2 and 5 (CO_2 range of 0.8%–5.3%), and in swine 5 the color changed to B after the third breath. In swine 6, the FEF detector started with color B and changed to C after the first breath.

The color range recorded with tracheal intubation was C in all six swine except during two ventilations (CO_2 range of 4.2%–6.5%) before the induction of ventricular fibrillation (Table 2). The color range observed during CPR was B in swine 1, 3, 4, and 5 (CO_2 range of 0.8%–1.6%) and C in swine 2 (CO_2 range of 1.7%–1.8%). Cardiopulmonary resuscitation was started 15 min after the onset of ventricular fibrillation in swine 6, and the FEF color detector displayed the A color (CO_2 level of 0%) during all six ventilations.

Discussion

The two most important characteristics of an ideal monitor in assessing proper placement of an endotracheal tube are that it should be (a) fail-safe and (b) able to determine the exact position of the endotracheal tube rapidly. These two criteria are necessary because of the disastrous consequences associated with unidentified esophageal intubation, which still occurs despite the numerous methods of assessing correct placement of endotracheal tubes (3,10). Unidentified esophageal intubation was the most frequent cause of morbidity and mortality in the practice of anesthesia in the last 4 yr (1,2). The 76 deaths and 18 cases of brain and/or other damage, reported in the ASA closed claims study, attributed to esophageal intubation could have been avoided if an ideal monitor had been available (2).

Accurate and consistent color interpretation is central to the successful use of the FEF CO_2 detector. Wrong color interpretation, for example C (endotracheal tube in trachea, according to manufacturer) instead of A (endotracheal tube in esophagus), may be potentially life-threatening to the patient, especially when the vocal cords cannot be visualized. The manufacturer of the FEF CO_2 detector claims that the B and C color ranges represent a CO_2 range of 0.5% to <2% and 2%–5%, respectively. This study indicated that the B color was only matched with a frequency of 77% and A and C colors were chosen at a rate of 10% and 13%, respectively, with a CO_2 concentration range of 0.5% to <2.0%. At a CO_2 concentration between 2.0% and 2.5%, our blinded observers selected the color range A, B, and C with a frequency of 0%, 37%, and 63%, respectively. This discrepancy could be explained by the interpersonal variation in the color-matching process among the blinded observers. There was probably a subjective factor involved when they had to choose between color range A, B, and C whenever the color of the FEF indicator did not exactly match A, B, or C. It is possible that an intrapersonal variation also exists. This was not addressed because demonstrating its existence would not affect the conclusions of this study.

During esophageal ventilations with or without carbonated beverage in the stomach, a C color range was observed with more than one breath on four occasions. If one was totally dependent on the FEF detector to assess correct placement of the endotracheal tube, accidental esophageal intubations would probably have been missed during the initial six ventilations.

During CPR, the FEF detector correctly indicated only one (swine 2) of six properly intubated swine by displaying the C color. The B color, observed during the six tracheal ventilations in four swine (time taken ~30 s), is the "grey" area and indicates either a low cardiac output or a possible esophageal intubation. The recommendation from the manufacturer's algorithm is to administer another six ventilations (another 30 s) and to watch for any color change. If the color is still in the B range, one must then ascertain the correct placement of the endotracheal tube by some other means. This situation may not be common. Unfortunately, it happens and it represents a major disadvantage for the FEF detector because it is in those difficult situations that one needs a fail-safe method of determining correct placement of the endotracheal tube. During a worst case scenario, the vocal cords may not be visible, breath sounds are not easily audible, and a bronchoscope and/or a portable capnographic analyzer is not immediately available during resuscitation of a patient in cardiac arrest on the ward. Precious time (approximately 60 s) could be wasted in trying to determine endotracheal tube placement with the FEF detector, and this could have an influence on the outcome of resuscitation. Once placement of the endotracheal tube is correctly determined, the FEF might be useful in assessing the adequacy of CPR.

The main advantage of the FEF detector is that it is a portable semiquantitative capnometer devoid of electronics and, apart from the problem of color perception, has most of the attributes of a nonportable capnometer. It may be useful to monitor ventilation during patient transport provided one assumes the endotracheal tube does not slip into the esophagus. It has a few disadvantages. It cannot provide, from the color change observed, a display of CO_2 waveform, which sometimes is the first hint of an esophageal intubation. Although a normal CO_2 waveform observed during expiration is no guarantee that the endotracheal tube is correctly placed, an abnormal waveform may be the first indication of esophageal intubation. Its performance in detecting CO_2 level semiquantitatively was not satisfactory because of the interpersonal variation in color matching among observers. Most importantly, it could not detect an esophageal intubation nor confirm correct intubation under adverse conditions.

To conclude, our results suggest the FEF detector does not satisfy the criteria required of a monitor for assessing accurately and rapidly correct placement of the endotracheal tube. It does not have the attributes of capnography and cannot be relied on when the vocal cords are not visible during laryngoscopy.

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Mivacurium: Dose-Response Relationship and Administration by Repeated Injection or Infusion

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The dose-response relationship and neuromuscular blockade after infusion or repeated injection of mivacurium were studied in 65 patients in nitrous oxide-narcotic anesthesia. The ED_{95} (twitch tension) was determined in 45 patients by intravenous injection of a single bolus of 30, 39, 47, 54, or 60 μg/kg (9 patients per dose). Another 20 patients received an initial bolus of $2 \times ED_{95}$ followed either by an infusion started at 5% twitch recovery (i.e., 95% depression) and adjusted to sustain 95% twitch depression (n = 10) or by repeated injection of $0.6 \times ED_{95}$ whenever twitch tension had recovered to 25% of control (n = 10). Five patients in each of these two groups received 7 μg/kg of neostigmine at 25% twitch recovery, and the others recovered twitch tension spontaneously. The mean ED_{95} was 73 μg/kg. A $2 \times ED_{95}$ bolus was followed by complete twitch depression within 2.2 ± 0.7 min. The mean infusion rate resulted in $6 \pm 2\ \mu g \cdot kg^{-1} \cdot min^{-1}$. The ensuing recovery index was 6 ± 3 min. A 6 ± 2 min recovery index was found after up to 10 repeat injections given every 9 ± 3 min. There was no significant effect of neostigmine in both groups. In conclusion, the recovery indices after the infusion or repeat injection of near-equal doses of mivacurium were identical.

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Mivacurium is a new, short-acting, nondepolarizing muscle relaxant of the benzylisoquinoline type. It has a short duration of action that has been attributed to rapid breakdown by plasma cholinesterase (1,2). It has been used for sustained muscle relaxation during long surgical procedures as either repeated bolus injection or continuous infusion (2–6). Yet, none of these studies has directly compared both techniques of administration with respect to their mivacurium requirements and the characteristics of the recovery of neuromuscular transmission. It was the purpose of this study to provide such information based on a predetermined dose-response relationship.

Method

After approval of the study by the hospital ethical committee had been obtained, 65 adult patients scheduled for maxillofacial interventions of an anticipated duration of at least 2 h gave written informed consent to participate in the study. Inclusion criteria were age 18–70 yr, body weight 45–110 kg, ASA grades I–II, and serum plasma cholinesterase activity of at least 2.9 U/L. Women of childbearing potential were excluded, as were those patients with neuromuscular, hepatic, or renal disease or those taking medication known to interact with neuromuscular blocking drugs.

All patients were premedicated with flunitrazepam (1–2 mg) and hyoscine (0.5 mg) administered orally 1 h before induction of anesthesia. Anesthesia was induced intravenously with midazolam (70 μg/kg), fentanyl (5–6 μg/kg), and etomidate (200–300 μg/kg) followed by nasotracheal intubation without the use of a muscle relaxant. Anesthesia was maintained with 70% nitrous oxide in oxygen in a rebreathing circuit with mechanical ventilation adjusted for 4.5–5.5 vol% end-tidal carbon dioxide concentration. No halogenated inhaled anesthetics were used. Increments of fentanyl (0.05–0.1 mg) and midazolam (1–2 mg) were administered intravenously as seemed necessary on clinical grounds. Neuromuscular transmission was monitored by recording the evoked twitch tension of the left adductor pollicis muscle in response to supramaximal train-of-four stimulation (2 Hz every 15 s) of the ulnar nerve at the

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wrist via surface electrodes. Details of the recording system were described previously (7,8). Both anesthesia and the recording system were allowed to stabilize for at least 10 min until mivacurium was injected. For the dose-response study, the first 45 patients were randomly allocated to five subgroups of nine patients to receive a single intravenous dose of mivacurium of 30, 39, 47, 54, or 60 μg/kg. A dose-response curve was then established by regression analysis of the log dose and the probit of the resulting twitch depression (9). Responses of 0% twitch depression (T1) were assigned values of 1%. The ED$_{50}$, ED$_{75}$, and ED$_{95}$ were calculated from the regression line. Twice the resulting mean ED$_{95}$ was administered to the remaining 20 patients as an intravenous loading dose injected into a fast-running infusion over 5 s. After random allocation to two subgroups of 10 patients, neuromuscular blockade was maintained either (a) by increments of mivacurium (0.6 × ED$_{95}$) injected intravenously whenever the first twitch response of a train-of-four (T1) had returned to 25% or (b) by an infusion of mivacurium that was begun when T1 had attained 5% of its control value. The mivacurium infusion was started at a rate of 10 μg·kg^{-1}·min^{-1} and was adjusted every 3 min for 95% ± 5% depression of twitch tension (T1). After the last maintenance injection of mivacurium or after discontinuing the infusion, five patients in each group received 7 μg/kg of neostigmine intravenously when T1 had recovered to 25% of control, whereas in the others twitch tension was allowed to recover spontaneously.

The twitch recordings of these 20 patients were evaluated for the following variables: time from end of injection of mivacurium to maximum twitch suppression (time of onset); maximum twitch suppression after the initial dose; time from end of injection of the initial dose to recovery of 5% and 25% of control twitch tension (DUR5%$_{\text{init}}$, DUR25%$_{\text{init}}$); time from end of injection of the maintenance doses to recovery of 25% of control twitch tension (DUR25%$_{\text{maint}}$); time from end of infusion to recovery of 25% of control twitch tension (DUR25%$_{\text{infus}}$); time from end of injection of the initial dose to recovery of 25% of control twitch tension after the last maintenance dose or after the end of infusion (duration of clinical muscle relaxation); time from 25% to 75% twitch recovery (recovery index); doses of mivacurium infused over 15-min intervals (fractional doses); and doses of mivacurium administered by initial injection with consecutive infusion or repeated injection (total dose). The data are presented as mean with standard deviation (SD). Intergroup and intragroup comparison was performed by paired and unpaired Student's *t*-test, respectively. Patient data were compared by analysis of variance.

Table 1. Patient Data

Patient group	Age (yr)	Weight (kg)	Height (cm)	*n*
Dose response study				
30 μg/kg	43 ± 25	70 ± 10	174 ± 7	9
39 μg/kg	36 ± 16	65 ± 12	169 ± 6	9
47 μg/kg	38 ± 14	72 ± 12	174 ± 9	9
54 μg/kg	35 ± 17	73 ± 10	174 ± 7	9
60 μg/kg	43 ± 15	76 ± 17	176 ± 7	9
Infusion/injection study				
Infusion	33 ± 12	65 ± 12	173 ± 9	10
Repeated injection	41 ± 15	68 ± 15	171 ± 7	10

Values are mean ± SD.

Table 2. Spontaneous and Neostigmine (7 μg/kg)-Induced Recovery of Twitch Tension After Repeated Injection Versus Infusion of Mivacurium

			Recovery index	
	Dose$_{\text{total}}$ (μg/kg)	DUR5%$_{\text{init}}$ (min)	Spontaneous (min)	Neostigmine-induced (min)
Repeated injection	480 ± 130	13 ± 3	6 ± 2	7 ± 1.5
n	10	10	5	5
Infusion	740 ± 330	14 ± 3	6 ± 3	5 ± 2
n	10	10	5	5
P	NS	NS	NS	NS

DUR5%$_{\text{init}}$, time from end of injection of the initial dose to recovery of 5% of control twitch tension; NS, not significant.
Values are mean ± SD.

Results

All groups of patients were not significantly different with respect to age, body weight, and height (Table 1). In the dose-response study, 30 μg/kg of mivacurium failed to produce any twitch depression in four patients. The most profound twitch depression (94%) was observed with 60 μg/kg. The ED$_{50}$, ED$_{75}$, and ED$_{95}$ values calculated from the log-probit regression line were 48, 62, and 73 μg/kg, respectively. After administration of an intravenous bolus dose of mivacurium (2 × ED$_{95}$) the time of onset was 2.2 ± 0.7 min, whereafter the twitch response was completely abolished in all 20 patients.

The resulting DUR5%$_{\text{init}}$ did not show a significant difference between the infusion and the repeat injection group (Table 2). The manual adjustment of the infusion of mivacurium allowed neuromuscular blockade to be maintained between 90% and 98%, with a resulting infusion rate of 6 ± 2 μg·kg^{-1}·min^{-1} (range 4–9 μg·kg^{-1}·min^{-1}) administered over 100 ± 30 min (range 55–140 min). Within this average, the dose fraction of mivacurium infused during the first 15 min

Table 3. Fractional Maintenance Doses of Mivacurium Infused for 95% Neuromuscular Blockade as a Function of Time

	0–15 min	15–30 min	30–45 min	45–60 min	60–75 min	75–90 min	90–105 min	105–120 min
Dose (μg·kg^{-1}·min^{-1})	9 ± 2	6 ± 3	5 ± 3	5 ± 3	6 ± 3	6 ± 2	6 ± 2	6 ± 2
n	10	10	10	10	8	6	6	4

Values are mean ± SD.

Table 4. Duration of Action of Maintenance Doses of Mivacurium (0.6 × ED_{95} = 44 μg/kg) Injected Intravenously Upon 25% Recovery of the Evoked Twitch Tension After an Initial Dose of 2 × ED_{95} (146 μg/kg)

	Maintenance									
	1	2	3	4	5	6	7	8	9	10
DUR25%$_{maint}$ (min)	9 ± 3	9 ± 3	9 ± 3	9 ± 2	9 ± 2	9 ± 2	9 ± 2	9 ± 3	9 ± 3	9 ± 3
n	10	10	10	10	8	7	7	5	3	3

was 30% more ($P < 0.005$) than all following 15-min fractions (Table 3). Twitch tension began to recover 2.4 ± 1 min after the end of infusion, from which point 6 ± 2 min elapsed until the twitch tension attained 25% of control (DUR25%$_{infus}$). The overall duration of clinical muscle relaxation after initial injection with consecutive infusion was 118 ± 28 min. The 6 ± 2 min recovery index was not significantly affected by 7 μg/kg of neostigmine (Table 2).

In the 10 patients of the repeat bolus injection group, the DUR25%$_{init}$ was 18 ± 5.0 min, which is 5 min longer than the DUR5%$_{init}$ and twice as long as the DUR25%$_{maint}$ (Table 4). The maintenance doses of mivacurium represented an equivalent of 5 ± 1.3 μg·kg^{-1}·min^{-1}, not significantly different from the requirements by infusion. The average 9-min DUR25%$_{maint}$ was constant within up to 10 injections (Table 4). The duration of clinical muscle relaxation (90 ± 36 min) was not significantly different from the corresponding value of the infusion group. Similarly, the average recovery index (Table 2) was the same as after infusion, also with no significant change after the injection of neostigmine (7 μg/kg).

Discussion

With respect to the short duration of action of mivacurium, previous workers established the dose-response relationship by means of the single-injection technique rather than by the cumulative method commonly used with muscle relaxants of long or intermediate duration of action (9). The possibility of higher ED_{95} values of short-acting muscle relaxants generated by the cumulative method relative to the single-injection technique has been discussed by Gibson et al. (10,11). We were also using the single-injection technique, which yielded an average ED_{95} within the range of 58–80 μg/kg as reported in the literature (3,4,12,13). Thus, mivacurium has about 0.8 times and 4 times the neuromuscular blocking potency of vecuronium and atracurium, respectively (14).

The onset of the initial dose of mivacurium found in our study was about 1 min faster than reported by Choi et al. (3.3 ± 0.9 min) and Savarese et al. (3.3 ± 0.6 min) who used approximately the same dose (150 μg/kg) (2,15). The slower onset of 4.8 ± 1.6 min found by Ramsey et al. (16) may be due to the electromyogram being used to quantitate neuromuscular blockade rather than the twitch tension (17). No such specific explanation apart from population variability can be proposed for the time of onset being 1.1 min shorter in our patients than in those of Choi et al. (15) and Savarese et al. (2).

Our DUR25%$_{init}$ of mivacurium is in agreement with the corresponding figures of previous communications (Choi et al. 15.5 ± 3 min; Savarese et al. 16.8 ± 3.3 min) (2,15), as is the constant duration of action of the maintenance doses (2,18). After an initial dose of mivacurium (150 μg/kg), Caldwell et al. (18) gave up to 10 repeated doses of 100 μg/kg. The intervals between the maintenance doses, which in their study were injected at a recovery level of 10% of control twitch tension, were also constant in six patients, whereas there was an up to 8-min increase in two others. This discrepancy suggests that the repeated doses used by these authors, which were as much as 2.3 times higher than ours, were probably greater than those sufficient to just sustain a given degree of neuromuscular blockade.

In an earlier study with vecuronium, the infusion resulted in an increase of 70% in the average recovery index relative to the repeated injection of a comparable dose (19). This finding could not be confirmed using mivacurium, neither in the present study nor by previous authors (2,4,5,12,20). These workers found recovery indices after mivacurium infusion close to ours, although their doses varied between 4.8 and 8.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The only exception is a study of Shanks et al. (6), where after an initial intravenous dose of 150 μg/kg and a subsequent infusion (6.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$), the recovery index was 4 min longer than after the initial dose alone (6 ± 2 vs 10 ± 7 min). Further studies are needed to determine whether the figures of Shanks et al. (6) reflect a dose-dependent recovery index as previously described with pancuronium (21). This, however, seems unlikely from our present state of knowledge. The average 6-min time from the end of infusion of mivacurium to 25% twitch recovery (Table 2) relative to some 20 min after vecuronium infusion (19) is particularly favorable to mivacurium's clinical use.

Savarese et al. (2) and Caldwell et al. (18) demonstrated that neostigmine (45 and 60 μg/kg) accelerated the recovery from mivacurium-induced neuromuscular blockade, whereas in our study 7 μg/kg was ineffective. Yet, the same small dose (0.5 mg per patient) reversed a 30% vecuronium neuromuscular blockade in a patient with myasthenia gravis (22) and achieved a 33%–70% reduction of the recovery index in vecuronium (n = 10) and atracurium (n = 10) neuromuscular blockade in healthy individuals (unpublished data). The near-equal recovery indices in our patients with and without neostigmine may therefore be attributed to the spontaneous recovery from mivacurium-induced neuromuscular blockade occurring faster than the 7–10 min onset of neostigmine (23). It may be expected that, in clinical practice, the use of anticholinesterase drugs after the use of mivacurium will rarely be required. We have not yet observed such cases.

In conclusion, our study confirmed the short duration of mivacurium neuromuscular blockade in clinical doses. Both infusion and repeated injection of mivacurium do not require significantly different doses per hour to provide clinical muscle relaxation whereafter the recovery indices are equal.

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REVIEW ARTICLE

Anesthetic Considerations for Laser Surgery

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Laser is an acronym for Light Amplification by Stimulated Emission of Radiation. This article will review relevant highlights of the physics of lasers and laser light, rationales for the variety of lasers in clinical use, and important anesthesia-related concerns during laser surgery.

Physics of Laser Light

Visual light is electromagnetic radiation, just as are radio waves, x-rays, and γ-rays. These different classes of electromagnetic radiation simply occur at very different wavelengths. Einstein explained that all electromagnetic radiation (e.g., light, radio, x-ray) consisted of wavelike quanta called photons that

1. Contain energy proportional to their vibrational frequency,

$$E\ (\mathrm{J}) = h\nu,$$

where J is joules, h is Planck's constant = 6.63×10^{-34} (J-s), and ν is the frequency of the photon in cycles per second;

2. Propagate without diminution in vacuum at 299,800,000 m/s,
3. Have a wavelength (λ) that can be calculated as

$$\lambda\ (\mathrm{m}) = \frac{2.998 \times 10^{8}\ (\mathrm{m/s})}{\nu\ (\mathrm{Hz})}.$$

The wavelength for visible light ranges from 385 nm (nanometers, 10^{-9} m) to 760 nm; shorter wavelengths are ultraviolet, longer are infrared.

Laser light differs from ordinary light in three ways. First, it is highly monochromatic. Laser light consists of photons that have a well-defined, very narrow band of wavelengths, whereas ordinary light contains a wide spectrum of wavelengths. Second, laser light is coherent. Coherence implies that the electromagnetic fields of all photons in the laser beam oscillate synchronously in identical phase. In ordinary light, the electromagnetic fields are phased randomly, even at the same wavelength. Third, directed beams of laser light are collimated, i.e., have minimal dispersion. The light remains in a narrow, collimated beam, whereas ordinary light beams spread out in all directions from a source point. These three characteristics allow lasers to generate intense light beams, to send such beams efficiently and accurately through lenses, and to deliver intense energy to small target sites.

Laser System Hardware

The essential components of a laser system include a lasing medium that holds the atoms whose electrons create the laser light; resonating mirrors to boost lasing efficiency; and an energy source to excite or "pump" the lasing atoms into producing laser light (Figure 1). The different types of lasers used in clinical practice use a variety of lasing media and energy pumps. Some lasers use a gaseous lasing media such as CO_2, argon, krypton, or helium-neon, and are pumped by electric discharge through the gas. Gas lasers may produce either a continuous or intermittently pulsed beam output. Other lasers use solid rods of laser-passive material containing small quantities of ionic impurities, known as dopants, that are the actual lasing material. Dopants commonly used for their laser potential include chromium (as in the ruby laser), neodymium (Nd), or holmium (Ho). A synthetic gem crystal known as YAG (yttrium-aluminum-garnet) is commonly used as a passive host matrix, but even glass has been used. Solid lasers are usually pumped by high-energy photons from a xenon flash lamp, and therefore produce a pulsed beam. Lasers also can be made from liquid dyes and semiconductors, but these technologies have yet to appear in a significant way in surgical practice. Some medically relevant lasing media and their respective output wavelengths are listed in Table 1.

Frequency doublers convert laser light to a different wavelength, enhancing therapeutic flexibility. A beam of laser light passed through a crystal of potas-

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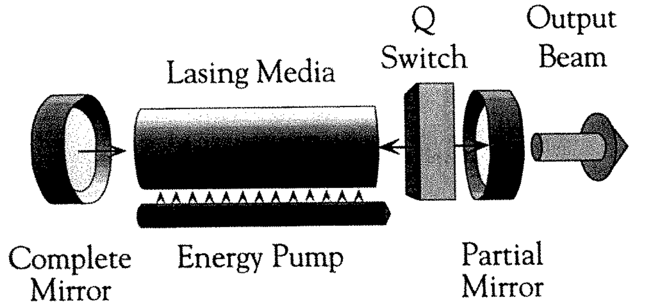

Figure 1. Generic laser hardware. A laser system consists of several components, irrespective of whether the laser is solid-, liquid-, or gas-based media. The central component is the lasing media itself. This may, for example, be a solid crystal of YAG with a small concentration of neodymium, or a tube containing carbon dioxide. The energy pump provides the means of obtaining a population inversion (see text) of orbital electrons; it may consist of a xenon flash lamp or an electric spark generator. A pair of axial mirrors allow repeated passes of collimated photons through the media, allowing maximum amplification by stimulated emission. The mirror on the right is not 100% reflective, allowing the beam to eventually escape. The optional Q-switch increases efficiency of pulsed lasers by allowing a small delay to increase the pumping.

sium-titanyl-phosphate (KTP) will emerge with a mixture of the original wavelength and a wavelength one-half of the original (double the frequency). In medical lasers, KTP is most often used with Nd-YAG. Truly tunable lasers now exist, but are still relatively low-powered devices.

A *light guide* directs the laser beam to the surgical site as illustrated in Figure 2. Fiberoptic bundles are a convenient, flexible conduit for visible and near-infrared wavelengths. Wavelengths outside this range, such as the long infrared from a CO_2 laser, require either an articulated arm containing front-surface mirrors at each joint or newly developed exotic materials in a fiberoptic bundle. Once the laser beam is delivered in proximity to the surgical site, it is either focused to the site by the lens of an operating microscope, or the shape of the beam can be intentionally altered by passing it through a contact probe directly on the tissue to be lasered.

Table 1. Laser Media Wavelengths

Laser media	Color	Wavelength (nm)
Carbon dioxide	Far infrared	10,600
Erbium-YAG	Infrared	2,930
Holmium-YAG	Infrared	2,060
Neodymium-YAG	Near infrared	1,064
Ruby	Red	694
Krypton	Red	647
Helium-neon	Red	632
Gold (vapor)	Red	632
Organic dye (liquid)	Red	632
Organic dye (liquid)	Yellow	585
Copper (vapor)	Yellow	578
Organic dye (liquid)	Yellow	577
Krypton	Yellow	568
KTP-Nd-YAG	Green	532
Krypton	Green	531
Argon	Green	515
Copper (vapor)	Green	510
Organic dye (liquid)	Green	504
Argon	Blue	488
Xenon fluoride	Ultraviolet	351
Xenon chloride	Ultraviolet	308
Krypton fluoride	Ultraviolet	248
Krypton chloride	Ultraviolet	222
Argon fluoride	Ultraviolet	193

An operating microscope accurately aims a laser by directing a low-powered ($\approx$1 mW) visible beam, usually from a low-powered He-Ne gas laser, through the same optical path as the surgical laser. Some surgical lasers can be focused to a spot size of 30 μm (0.030 mm), creating very high power densities.

For surgical procedures that do not require a "no-touch" technique, there are special heat-resistant (sapphire) direct-contact probes (1) (Figure 2) that are replaceable and can be designed for sharp cutting or diffuse coagulation as needed. These probes require active cooling in the form of a compressed gas or liquid jet, a feature that has become responsible for significant recent laser-related morbidity and mortality (2). The mechanism of action of the contact probe is probably a combination of thermal conversion within the sapphire (heating the surface to >800°C) of most of the laser energy and transmission of perhaps 20% of the near-infrared energy to the surrounding tissue (3).

Clinical Applications

Lasers are now used as scalpels and electrocoagulators with some unique advantages. For example, lasers allow highly precise microsurgery, even in confined or difficult-to-reach locations. The ability to focus laser beams on small target areas concentrates the intensity or power per area enormously. For example, a 10-W beam, originally 1 cm^2 in area, would have a power density of 10,000 W/cm^2 when focused on a target area of 0.001 cm^2. This power density delivers approximately 2500 calories per second to the target site, producing heating at a rate of many thousand degrees per second, depending on the volume of energy absorption. This energy delivery allows precise, rapid vaporization of tissue, or indeed most materials save metals and ceramics. Lasers do not increase the energy of a particular photon, but simply can place more photons of the same energy at a given place and time than other light sources. Laser surgery is relatively "dry," providing near instantaneous sealing of small blood vessels and lymphatics, even in the presence of

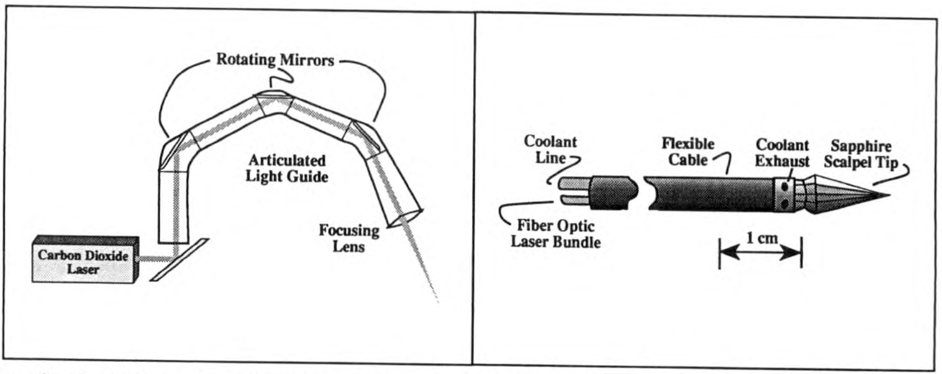

Figure 2. Light guides. On the *left* is a schematic representation of a CO_2 laser guide as might be found in either an operating microscope or a hand-held wand. The guide consists of rigid hollow tubes with hinged, aligned mirrors that reflect the beam from its source through the focusing lens. On the *right* of the figure is a schematic of a flexible fiberoptic guide with a sapphire contact scalpel and a coaxial cooling system.

clotting abnormalities; however, early claims for faster than normal healing and lower infection rates have not been validated.

Laser Interaction With Tissue

Living tissue is a complex aqueous solution containing a variety of molecules that absorb light. When an atom interacts with a photon whose energy does not exactly match a possible electron transition, its energy may be translated into atomic vibrations we recognize as heat. The degree to which a particular wavelength of light is absorbed and converted to heat in the tissue of interest will determine its effect on that tissue. Long infrared wavelengths are absorbed with great efficiency by water, the main constituent of tissue. Therefore long-wavelength laser light, like that from CO_2 (operating at 10,600 nm), is completely absorbed by water in the first few layers of cells. With powerful, focused CO_2 beams, this leads to explosive vaporization of the tissue surface at the target with surprisingly little damage to underlying tissue. The new excimer lasers produce ultraviolet light that is even more intensely absorbed by water and other molecules and thus has an even more superficial effect. Near-infrared light from an Nd-YAG laser at 1064 nm is much less absorbed by water, and the beam is transmitted and scattered through a volume of tissue perhaps 100–1000 times the volume through which a CO_2 beam diffuses. Consequently, the energy of an Nd-YAG beam is more widely disseminated (Figure 3), producing less vaporization and more thermal coagulation (i.e., a cooking effect). Some of the effects of this beam may not be apparent for hours or days after exposure. Red light, as from a ruby laser (694 nm), is poorly absorbed except by cells containing dark pigment. The green and blue light produced by argon (488 and 514 nm, respectively) or krypton (476, 521, and 568 nm) gas lasers is transmitted by water, but intensely absorbed by hemoglobin, providing the ability to penetrate skin or ocular structures and selectively coagulate vascular or pigmented regions. Although lasers that produce infrared or visible light have exclusively thermal effects on tissue, the photons produced by ultraviolet excimer lasers are energetic enough to directly disrupt chemical bonds and cause ionization, which in turn can lead to mutation and carcinogenesis.

Risks of Laser Use

Standards and Regulations

Because they are potentially dangerous technologic devices, the medical use of lasers is subject to both some degree of federal regulation and to voluntary consensus standards to minimize possible risks. The

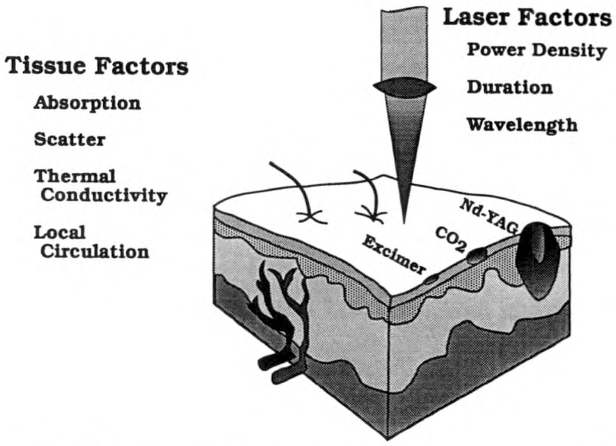

Figure 3. Different wavelengths of laser light cause different patterns of tissue destruction. The actual destructive effect of laser light on tissue depends on both laser parameters and tissue factors.

U.S. Food and Drug Administration (FDA) controls the manufacture and marketing of medical laser equipment. There are presently no mandatory federal regulations governing the clinical use of or safety precautions for lasers. The current standard to which institutions that use lasers should subscribe is the *American National Standard for the Safe Use of Lasers in Health Care Facilities* (Z136.3-1988) published by the American National Standards Institute (ANSI). (ANSI Z136.3-1988 is available from the American National Standards Institute, Inc., 1430 Broadway, New York, NY 10018, or from the Laser Institute of America, 5151 Monroe Street, 102W, Toledo, OH 43623.) This document represents a consensus of governmental, industrial, and professional authorities on the methods used to define and control the risks of laser use, to define and standardize training, and to assess and ensure safety. Several states have adopted variations of a set of regulations suggested by the FDA (4), and the U.S. Occupational Safety and Health Administration (OSHA) is empowered to intervene if the medical use of lasers threatens the health of employees. Although patients are at most risk from the surgical use of lasers, injuries to staff have not been rare. The safety guidelines proposed by both the ANSI and the FDA should be followed to the maximal extent possible.

Manufacturers are presently required to report unusual incidents or injury as they become aware of them. Clinicians, however, are required to report complications due to laser use only when they occur in the course of a premarketing testing protocol; at other times, clinical reporting is voluntary. Consequently, the true incidence of laser injury is not known with certainty. The passage by Congress of the Safe Medical Devices Act of 1990 will require reporting by clinicians of all serious injuries and should provide more accurate data regarding the prevalence of such injuries.

Laser Hazards

The hazards owing to laser use can be separated into four major categories: atmospheric contamination, perforation of a vessel or structure, embolism, and inappropriate energy transfer. There were 21 injuries reported to the FDA between January 1989 and June 1990, two were minor, 12 were serious, and there were seven mortalities (5). The distribution by type of injury is illustrated in Figure 4.

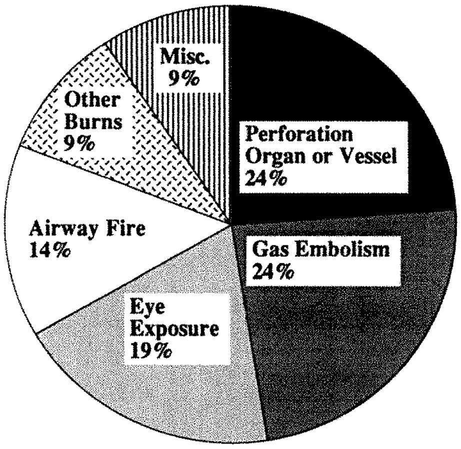

Figure 4. Distribution of laser-injury type reported to the FDA 1/89–6/90. Data from Reference 5.

Atmospheric contamination. Vaporization of tissue, whether by electrosurgery or laser radiation, produces a plume of smoke and fine particulates (mean size 0.31 μm; range of sizes 0.1–0.8 μm [6]). The size of these particles falls within the range that is efficiently transported and deposited in the alveoli. Many individuals find the odor of this plume objectionable, and sensitive individuals have described headaches, tearing, and nausea as a consequence of inhalation. Deposition of laser plume particulates in rat lung appears capable of producing interstitial pneumonia, bronchiolitis, reduced mucociliary clearance, inflammation, and emphysema (7,8). Laser plume also has the potential to be mutagenic (9), teratogenic, or a vector for viral infection. In vitro, the mutagenic potential of laser condensate is half that of electrocautery (10), and the total mutagenic potential from 1 g of tissue is comparable to that from smoking three to six cigarettes. The role of the smoke plume as a viral vector is controversial: viral DNA has been detected in plumes from condyloma [11,12] and skin warts (13), but not from laryngeal papilloma (14). The presence of HIV in laser plumes from infected tissue has yet to be addressed, although HIV was not detected in electrosurgical smoke plumes (15). Competent transmission of any viral infection via smoke plume has yet to be demonstrated. Laser plume does not appear to contain viable eukaryotic cells (i.e., tumor cells [16,17]) but may contain viable bacterial spores (18,19).

CO_2 lasers seem to produce the most smoke owing to the vaporization of tissue; Nd-YAG contact probes, much less. The most effective means of preventing dissemination of the plume is with an efficient smoke evacuator at the surgical site (20,21). Ordinary surgical masks efficiently filter particles down to about 3.0 μm; therefore special high-efficiency masks (i.e., The Protector II, Anago, Fort Worth, Tex.) are needed to catch laser plume particulates. These high-efficiency masks lose their efficiency when wet and may need to be changed periodically.

Perforation. Misdirected laser energy may perforate a viscus (22) or a large (uncoagulable by laser, >5 mm) blood vessel. Laser-induced pneumothorax after a laryngeal procedure also has been reported (23). The depth of damage is impossible to judge accurately when using an Nd-YAG system, and perforation may occur several days postoperatively when edema and necrosis are maximal.

Embolism. Venous gas embolism may occur during laparoscopic laser surgery, but has been a particular problem during hysteroscopic surgery with Nd-YAG contact probes when the gas coolant for the sapphire probe tip has accidentally inflated the uterine cavity. This technique resulted in five widely publicized cases involving four deaths in 1989 (2). The contact probe itself is not required for injury; a fatal gas embolism during uterine insertion of a sheathed quartz fiber (with coaxial coolant gas running) produced an immediate massive embolism (24). For this reason, during hysteroscopy, liquid (saline) coolant is the only safe option. If coolant gas must be used, using carbon dioxide will result in the least damage after an embolization when compared with either nitrogen or air. If saline is used instead of gas for uterine distention, a fluid overload similar to that seen during transurethral prostate surgery is possible (25). Venous gas embolization has also been reported during Nd-YAG resection of tumor in the trachea (26,27) and during various types of laparoscopic procedures. Recently, a laser coolant malfunction during laparoscopic ablation of endometriosis lesions at the author's institution resulted in complete, subcutaneous, air emphysema from which the patient recovered after a benign course. During laparoscopic surgery with CO_2 insufflation, mechanical hyperventilation should be instituted to compensate for intra-abdominal CO_2 absorption and cephalad displacement of the diaphragm. Continuous airway CO_2 monitoring is highly recommended for detection of either embolization or hypercapnia.

Energy transfer to an inappropriate location. All available medical laser light is transmitted transparently through air and is well reflected by smooth metal surfaces. Pressing the laser control trigger at the wrong time can deliver damaging laser light across the wound to sites where surgical ablation was not desired, or across the operating room into someone's eyes. Potentially tragic scenarios include laser ignition of surgical drapes (28) (Figure 5) and, of special interest to anesthesiologists, accidental irradiation of an endotracheal tube during airway surgery.

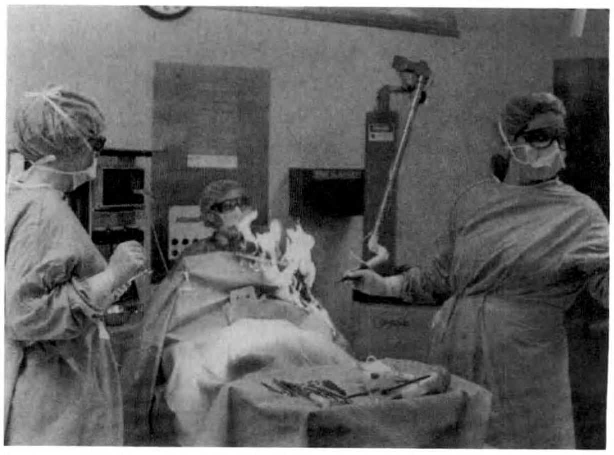

Figure 5. Surgical drape fire from an accidentally misaimed laser pulse. Reproduced with permission of Health Devices and the Emergency Care Research Institute, from Airway fires: reducing the risk during laser surgery. Health Devices 1990;14:109.

Eye Protection

The ANSI standard as well as common sense dictates that eye protection be used by all operating room staff and the patient during the conduct of laser surgery. Errant infrared energy from a CO_2 laser can quickly cause a serious corneal injury (29), whereas argon, (KTP) Nd-YAG, or ruby lasers are more likely to burn the retina (30). Patients' (nonoperated) eyes should be taped so the lids are closed, then covered with an opaque, saline-soaked knit or metal shield (31–33). Operating room personnel must wear safety goggles or lenses that are specific for the laser wavelength in use. Safety goggles should provide wrap-around protection from reflected light. For CO_2 lasers, any clear glass or plastic lenses will suffice because they are opaque to far-infrared light. Regular eyeglasses can be sufficient, but contact lens are not. Other lasers require color filters whose wavelength specificity and optical density are regulated. Nd-YAG lasers require either special green-tinted goggles, which make assessment of patient skin color difficult, or newly available clear lenses (Nd:YAG Protection Glass, Surgical Laser Technologies, Malvern, Pa.) with a special coating opaque to near-infrared light. Argon or krypton lasers require an amber-orange lens filter, and KTP-Nd-YAG lasers require a red filter. As lasers other than the CO_2 produce beams that pass through glass, all windows into the operating room should be covered during laser procedures and warning signs should be posted as described in ANSI Z136.3.

Endotracheal Tube Fires

A feared complication of laser use during airway surgery is endotracheal tube fire. The estimated inci-

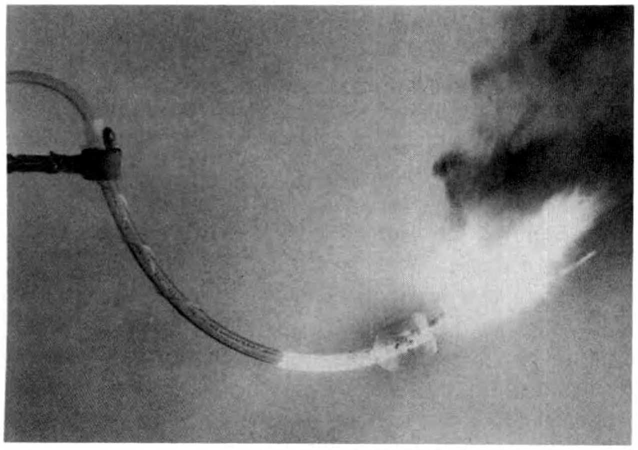

Figure 6. Blowtorch ignition of an endotracheal tube. Reproduced with permission of Health Devices and the Emergency Care Research Institute, from Airway fires: reducing the risk during laser surgery. Health Devices 1990;14:109.

dence of this complication during such operations is 0.5% (34)–1.5% (35). A mail survey of otolaryngologists, although not providing an incidence for fires, did demonstrate that laser-induced ignition of endotracheal tube, cuff, or cottonoids was responsible for the majority (41%) of perioperative complications, followed by postoperative laryngeal web (19%) and laser-related/induced facial burn (11%) (36). The largest published (retrospective) series of CO_2 laser airway surgery documented 6 of 4416 cases (0.14%) of airway fire (37), confirming it as the most frequent laser-related complication in this group of patients. Given the proximity of the endotracheal tube to surgical sites around the larynx, the potential for fire or other airway complications is clear. Most of these fires, when appropriately handled, result in minimal or no harm to the patient (34,38,39), but catastrophic consequences are possible (40,41). With the energy delivery rates described earlier, any hydrocarbon material, including tissue, plastic, and rubber, can ignite and burn, particularly in an oxygen-enriched atmosphere. Fires can result from direct laser illumination, reflected laser light, or incandescent particles of tissue blown from the surgical site (42). Initially, most fires are located solely on the external surface of the endotracheal tube where they can cause local thermal destruction. If the fire is unrecognized and burns through to the interior of the tube, then the oxygen-enriched gas and flow owing to ventilation will produce a blowtorch-like flame blowing heat and toxic products of combustion down to the pulmonary parenchyma (Figure 6). Puncturing and deflating the tube cuff may permit oxygen-enriched gas to flood the operative site and increase the chance of a devastating fire after a subsequent laser burst.

Three approaches have been developed to reduce the incidence of airway fire: (a) reduce the flammability of the endotracheal tube; (b) use Venturi ventilation; or (c) use intermittent apnea. Each of these will be discussed.

Relative flammability. Given that all common endotracheal tubes are potentially flammable, considerable effort has been expended to assess the relative risks of the various types of construction material. For many years, reusable red rubber tubes were commonplace, then were eventually supplanted by clear polyvinylchloride (PVC) plastic tubes. Modern PVC strongly absorbs far-infrared light and is thus very sensitive to CO_2 laser energy. Polyvinylchloride tubes appear to be much more easily ignited by CO_2 lasers than red rubber tubes (37,43,44) and to produce more toxic combustion products. In vitro, PVC is transparent, and thus immune to Nd-YAG and visible laser light; however, a thin coating of mucous or blood in vivo will absorb energy and restore the hazard. Two recent studies of the effects of Nd-YAG laser energy on common types of tubes, including those designed to be resistant to laser light, revealed that endotracheal tubes of all materials are in fact quite vulnerable (45,46). Ossoff et al. (43) compared the extent of acute damage to the trachea from blowtorch-type ignitions in dogs receiving 1% halothane and 70% nitrous oxide (balance oxygen) through PVC, rubber, or silicone endotracheal tubes. They reported easiest ignition in the case of PVC, followed by intense flame, widespread deposit of carbonaceous debris, and significant postmortem ulceration and inflammation of the trachea. Red rubber tubes were more resistant to ignition and produced less debris and inflammation. Silicone tubes were the most resistant to ignition but produced copious white silica ash, leading the authors to speculate about potential late silicosis. In a subsequent study (47), Ossoff measured the time to intraluminal ignition during exposure to CO_2 laser energy to determine resistance to ignition and reversed the ranking of silicone and red rubber, with PVC remaining the most vulnerable. He also found that the addition of 2% halothane vapor retarded ignition. The index of flammability once ignition occurs is the minimum necessary fraction of inspired oxygen (F_{IO_2}) to maintain combustion. Wolf and Simpson (48) concluded that PVC is actually less flammable than silicone or red rubber, having a flammability index of 0.26 versus 0.19 or 0.18 for silicone and red rubber, respectively. When nitrous oxide was used as the oxidant, PVC retained the highest index (0.46), followed by silicone (0.41) and red rubber (0.37).

Despite the conflicting data, many authors recommend the use of red rubber endotracheal tubes during laser surgery of the aerodigestive tract, basing this suggestion on criteria of resistance to ignition and least toxic combustion products. However, at the University of California, San Francisco, one surgeon has performed 4000 microdirect laryngoscopies using a CO_2 laser with two fires (0.005%), and no significant fire-related morbidity (personal communication, H.H. Dedo) using foil-wrapped PVC endotracheal tubes and moistened pledgets.

Regardless of the tube substrate material chosen, there are additional safety considerations and maneuvers to consider; these are outlined below.

Effect of high oxygen or nitrous oxide gas mixture. The mixture of airway gases becomes an important issue when any type of potentially flammable endotracheal tube is used. Combustion is more vigorous when excess oxidizer is present, and most clinicians recognize the need to reduce the FIO_2 below 0.40 or to the minimum concentration consistent with patient oxygenation. That nitrous oxide is also a powerful oxidizer is less well recognized, but adding nitrous oxide as a diluent for oxygen is just as dangerous as having a high FIO_2 (48). Using an air/oxygen mixture appears to be acceptable. Some investigators prefer helium as a diluent to nitrogen because helium has a higher thermal conductivity and may delay the ignition of an endotracheal tube for a few seconds (47,49). The index of flammability is only reduced 1%–2% when oxygen/helium is substituted for oxygen/nitrogen (50). Helium also has a lower viscosity and will allow the use of a smaller endotracheal tube without turbulence and high resistance to flow (51,52).

The volatile anesthetics currently used in clinical practice are nonflammable and nonexplosive in clinically relevant concentrations (53,54). During an airway fire, however, they may pyrolize to potentially toxic compounds (55). Thus, the ANSI Z136.3 standard recommends not using volatile anesthetics during airway laser surgery. This is an extremely conservative stance given the low concentration of anesthetic gas compared with the products of combustion from an endotracheal tube and the lack of evidence of toxicity owing to the pyrolytic products. In cases where Venturi ventilation is used, administration of volatile agents is not usually mechanically possible.

Protective taping. Once the specter of endotracheal tube ignition was raised, extrinsic protection of the tubes was suggested (56). Patil and colleagues suggested wrapping tubes with moistened muslin (57). If allowed to dry, the muslin would become flammable. Kumar and Frost (58) suggested coating the vulnerable portion of the exterior of the tube with dental acrylic. This approach, however, renders the tube rigid with a rough surface that may traumatize the mucosal surfaces. Perhaps the most popular approach to the problem has been wrapping the tube with metalized foil tape (35,44,45,47,56,59,60). Three types of tape have been used: aluminum foil with adhesive backing, copper foil with adhesive backing, and a plastic tape that is thinly metalized on one side and has adhesive on the other. These tape products are widely available from retail electronics, arts and crafts, or building supply shops. A similar-appearing product is the lead foil that is commonly used on windows for burglar alarms; this tape is toxic and should never be used. The aluminum and copper tapes have been assessed for their ability to protect different types of endotracheal tubes against a variety of lasers. Although taping cannot provide protection of the inflatable cuff portion of an endotracheal tube, these metal tapes can offer a measure of protection against inadvertent, unfocused CO_2 laser hits. Metal tape is a less certain shield against the near-infrared beam from a Nd-YAG laser. Sosis and Dillon (60) found that metalized plastic tape (i.e., Radio Shack #44-1155) was actually more incendiary than an unwrapped red rubber tube with a time to ignition (50 W, beam diameter = 0.68 mm) of 6 s versus 13 s for the unwrapped control. The solid copper (1 mil Foil from Venture Tape Corp., Rockland, Mass.) or aluminum (#425 or 433 from 3M Corp., Industrial Tape Division, St. Paul, Minn.) tapes were able to withstand at least 60 s of direct laser exposure without penetration or ignition. A recent study by Health Devices (61) also found that the metalized plastic tape, while most pliant and least likely to abrade the larynx, provided protection only for CO_2 lasers, not Nd-YAG or KTP-Nd-YAG lasers. The 3M aluminum tape provided protection against CO_2 and KTP-Nd-YAG lasers but did allow ignition of a PVC tube at the highest power setting of an Nd-YAG laser. Copper tape (#1181, 3M Corp., Electrical Products Division, St. Paul, Minn.) provided ignition protection from all three lasers.

If a metal foil wrap is chosen to be used for laser surgery, its application on the endotracheal tube requires some care. A clean tube should be wiped with alcohol to remove residue that would interfere with adhesion, and then optionally be wiped lightly with Mastisol (Ferndale Laboratories, Ferndale, Mich.) or tincture of benzoin. The end of the tape should be cut at an angle of about 60°, and the cut edge should be aligned with the proximal end of the cuff junction (Figure 7). A spiral wrap with approximately 30% overlap should continue at least to the exit point of the cuff pilot tube. Care needs to be taken to prevent wrinkles that might abrade the tracheal mucosa. There must be no windows of bare tubing or areas of exposed tape adhesive (which is quite flammable). Rewiping the wrapped tube with

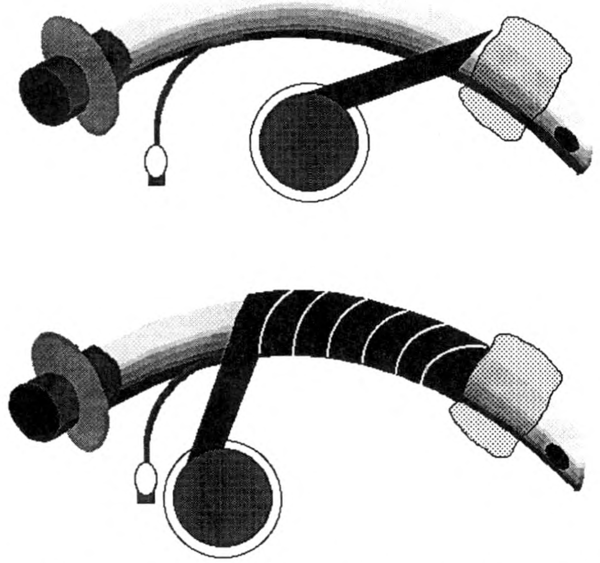

Figure 7. Cuff wrapping technique. If a wrapped endotracheal tube is the chosen method for laser protection, the technique for wrapping is critical in assuring both protection from ignition and from foil-induced mucosal abrasions. It is often helpful to first sparingly paint the tube with a medical adhesive like benzoin or Mastisol. The end of the tape should be cut with a scalpel to approximately 60°. Begin wrapping by aligning the cut end of the tape with the junction of the tube and the proximal end of the cuff. Wrap in a spiral with a 30%–50% overlap between layers. Wrap including the inflation tube for the cuff and continue until just short of the pilot balloon. Take care not to wrinkle the tape at any point.

alcohol will provide a degree of sterility before tracheal intubation.

Despite the fact that these metal foils have been shown to be relatively effective in this regard, the manufacturers have not pursued FDA review or approval as medical devices. Although it is not illegal for a physician to create and use a custom device such as a wrapped endotracheal tube, should an injury occur, the clinician's legal position as a noncertified "manufacturer" might be tenuous. Although the practice is well supported in the medical literature, there may have been less risk of liability before the advent of the FDA-approved commercial products described below.

A commercial, FDA-approved version of metallic foil wrap is the Merocel "Laser Guard" wrap (Merocel Corp., Mystic, Conn.). This laser-protective wrap has an adhesive metal foil with a synthetic sponge surface. When properly placed on an endotracheal tube and kept moist, the Merocel wrap provides protection against CO_2, argon, and KTP-Nd-YAG, but not YAG lasers (61). A potential disadvantage of this product is that the wrap adds almost 2 mm to the diameter of the endotracheal tube. Like the nonapproved wraps, this product can only be applied to the shaft of the tube and cannot provide any protection for the cuff.

Another commercially available, approved method of endotracheal tube protection is to make a laser-resistant coating an integral part of the tube. This type of tube is available as the Xomed "Laser Shield" tube that is fabricated from silicone with an outer layer of finely divided aluminum powder in silicone. The aluminized layer extends over the inflatable cuff. The manufacturer (Xomed-Treace, Jacksonville, Fla.) recommends this tube only be used with CO_2 lasers and a beam intensity of less than 4900 W/cm^2 and specifies that the F_{IO_2} be less than 25%. This endotracheal tube is more resistant to far-infrared radiation than either PVC or red rubber tubes (62,63), but the resistance is only relative and the tube will burn vigorously once ignited in vitro (47), producing friable silica dust. There has been at least one case report of an airway fire involving a Laser Shield tube (41). This case involved a serious injury owing to an intraluminal fire secondary to laser penetration of the cuff during a polyp excision with the power settings within specified limits but a high F_{IO_2} with balance nitrous oxide. The Laser Shield did not "pass" the Health Devices flammability test (61), igniting under typical surgical conditions.

When using potentially flammable endotracheal tubes, four guidelines should be remembered:

1. Minimize the F_{IO_2}
2. Use wet pledgets above the cuff after replacing the pledget string with wire; remoisten pledgets frequently
3. Use colored saline in the cuff
4. Place the cuff sufficiently distal in the trachea to be out of direct sight of the operator.

Metal endotracheal tubes. In 1978, Norton and De Vos (64) introduced a nonflammable endotracheal tube. The Norton tube is an interlocking stainless steel spiral coil resembling electrical cable armor. The tube walls are not airtight which, although allowing a cooling gas flow to the exterior surface, may make ventilation difficult in patients with relatively noncompliant lungs, particularly as this tube has no inflatable cuff. Jet ventilation with a modified Sanders Venturi coupler has been suggested as a means to overcome this problem (65). Another alternative is a separate, slide-on cuff, but these are all flammable and thus may present an ignition risk. This tube was available from Baxter Healthcare Corp (Niles, Ill.), but its manufacture was recently discontinued.

Two other metal endotracheal tubes are commercially available and approved for use with specific lasers. The "Laser Flex" tube (Mallinckrodt, St. Louis, Mo.) is an airtight stainless steel spiral with two distal, PVC saline-inflatable cuffs (redundant in case of puncture of the proximal cuff). This tube is resistant to CO_2 and KTP laser energy, but not Nd-YAG (61). The Bivona "Fome-Cuf" (Bivona, Gary, Ind.) is an aluminum spiral tube with an outer covering of silicone and a unique self-inflating foam-sponge-filled cuff. The foam in the cuff prevents collapse after puncture. This feature allows continued positive pressure ventilation and segregation of airway gases from the operative site, but may lead to injury if a puncture of the cuff or the filling tube prevents deflation before removal. The Fome-Cuf is only approved for use with pulsed CO_2 lasers. The use of laser-resistant endotracheal tubes requires particular care to prevent mucosal abrasions, because these tubes tend to be bulkier and more rigid than conventional tubes. The surgeon must also be careful that laser energy is not reflected off smooth metal surfaces and directed at sensitive structures. Finally, use of a metal endotracheal tube does not imply absolute protection from ignition as 50 W of Nd-YAG beam focused to 0.68 mm ignited a Laser Flex in 6 s (45).

Jet ventilation. Some authors contend that optimal surgical conditions and patient safety can be obtained with so-called "jet" ventilation. This technique takes advantage of Bernouilli's Venturi principle to augment the ventilation produced by a narrow stream of high-speed gas flow. In practice, jet ventilation uses an intermittent high-pressure oxygen supply, directed at the glottis through a small metal tube, like a ventilating bronchoscope, or even a 12-gauge blunt needle (66–71). Jet ventilation with air has also been used via a bronchoscope when resecting distal tracheal and bronchial tumors (72–75). It has been suggested that patients undergoing laser resections of airway tumors during jet ventilation may absorb carbon monoxide from entrained laser smoke in the pharynx. The carbon monoxide, in turn, would cause pulse oximetry to overestimate arterial oxygen saturation. Goldhill et al. (74) found neither a significant increase in carboxyhemoglobin during Nd-YAG bronchoscopy nor a difference in pulse oximeter reading versus in vitro cooximeter measurement of arterial oxygen saturation. Although jet ventilation generally provides adequate ventilation without introducing flammable material or a large obstacle to the surgical field, there are several potential disadvantages including the potential for barotrauma, pneumothorax, or crepitus; the restriction to only intravenous agents; gastric distention; and the relative requirement for compliant lungs.

To reduce obstruction of the surgical field by ventilatory instrumentation even further, several authors have advocated its complete removal, combined with the technique of spontaneous ventilation or intermittant apnea with general anesthesia provided by nasal insufflation or bronchoscopic delivery of a potent inhaled anesthetic (32,55,76,77) or an intravenous agent (78). Cohen et al. (79) and Hawkins and Joseph (80) have advocated modest hyperventilation followed by intermittent tracheal extubation by the surgeon for periods of 90–120 s during which the laser is used. Pulse oximetry adds a measure of safety by confirming adequate oxygenation from a denitrogenated pulmonary residual capacity during apnea.

Although not specifically related to laser procedures in the airway, it is prudent to be prepared to recognize and treat vagal hyperactivity, which is frequently seen in instrumentation of the trachea.

Airway fire protocol. Should an airway fire or explosion occur, the surgeon and anesthesiologist need to act quickly, decisively, and in a coordinated fashion. This may not be easy after an explosion, as the event may be so traumatic as to temporarily incapacitate the operating room staff. The key then, is communication and practice (at least a mental drill of the emergency procedure). Schramm and colleagues (81) have provided a useful review of the ensuing pathology and suggested emergent management.

Should a surgeon detect an endotracheal or other source of airway fire, he or she should as quickly as possible remove the source and simultaneously inform the anesthesiologist, who should immediately, despite reflexive training to the contrary, stop ventilation. It may be useful to temporarily disconnect the breathing circuit from the anesthesia machine. These maneuvers remove the flame and the retained heat in the tube as well as stop the enriched source of oxygen. The flaming material should be extinguished in a bucket of water that should always be available during laser cases. The patient should then receive mask ventilation with 100% oxygen, and anesthesia should be continued. A direct laryngoscopy and rigid (Venturi-ventilating) bronchoscopy should be performed to survey damage and remove debris. If the fire was an interior blowtorch type, then gentle bronchial lavage may be indicated, followed by fiberoptic assessment of the more distal airways. If any airway damage is seen, the patient should be reintubated. Fortunately, small exterior-only fires may not cause appreciable damage. If the damage is severe, a low tracheostomy may be indicated. The pattern of damage tends to be worst in the upper airway and diminishes as one approaches and passes the carina. The oropharynx and face should be assessed and a chest radiograph should be obtained. Pulmonary damage owing to heat and/or smoke inhalation may necessitate prolonged intubation and mechanical ventilation. A brief course of high-dose steroids may be helpful (82,83).

Lasers provide a useful new tool in the surgical armamentarium, one for which anesthesiologists must, with increasing frequency, prepare their patients and themselves. Although some of the potential threats posed by lasers are unique, most are simply extensions of the risks posed by the previous generation of surgical tools. As with most potentially dangerous procedures, the risks of laser use can be minimized by common sense and preconsidered contingency plans.

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Glossary

Ablation: Removal of tissue by vaporization.

Absorption: The transformation, by interaction with matter, of radiant energy to a different form of energy.

Active medium: A material that lases with the proper excitation.

Aiming beam: A very low-powered laser beam that is collimated with the high-powered, often-invisible therapeutic beam to illuminate the target site.

Angstrom (Å): 10^{-10} meter.

Anode: The positive terminal in a gas discharge laser.

Attenuation: The reduction in beam energy by absorption or scattering as it passes through matter.

Brewster windows: Transparent windows at the ends of a gas laser discharge tube set at an angle to the optical axis of the tube (Brewster's angle) so as to provide maximum light transmission.

Coherent light: Light in which the photons all have the same wavelength and maintain a constant in-phase relationship with each other.

Collimation: The property of a light beam that describes the degree to which the constituent photons move in a single direction. Highly collimated beams do not spread in diameter as they move away from the source.

CW: Continuous wave mode, a mode of operation in which the laser discharge is continuous.

Diffraction: The modulation in intensity and apparent bending exhibited by photons as they pass an opaque body.

Dopant: A chemical added to a crystal matrix to serve as an active lasing constituent.

Energy density: The amount of energy per unit area arriving at a surface. Usually noted in joules/cm^2.

Excimer: Exciter dimer, a type of laser based on the transition states of a diatomic molecule (e.g., ArF, KrF, or XeCl). These lasers produce very energetic photons.

Extinction length: The thickness of a specified media that absorbs 98% of the incident beam intensity, measured in cm^{-1}.

Infrared: Electromagnetic radiation with a wavelength in the band 0.7 μm–1.0 mm, i.e., longer wavelengths than visible light, but shorter than microwave/radio.

Interference: The phenomena of photons of like wavelength but different phase combining constructively and destructively to modulate the resulting intensity.

Joule: A unit of energy, 1 joule = 1 watt-second.

Micrometer, Micron, μm: 10^{-6} meter.

Mode: A description of the intensity cross-section of a laser beam.

Monochromatic: Light of a single wavelength or color.

Nanometer: 10^{-9} meter.

Neodymium, Nd: A rare earth metal that is frequently chosen as a lasing material within a substrate of glass or YAG.

Output power: The rate of energy discharge, usually watts or joules/second.

Photon: A quantum of electromagnetic energy possessing both wavelike and particlelike properties. Photons travel at a constant 299,800,000 m/s.

Power density: The amount of power (energy per second) per unit area arriving at a surface. Usually noted as watts/cm^2.

Pulsed mode: A mode of operation in which the laser delivers discrete (usually quite brief) bursts of photons.

Pump: The means of inducing an electron population inversion so that stimulated emission might occur.

Resonator: The combination of lasing material and mirrors necessary to support laser activity.

Spontaneous emission: The emission of a photon when an excited orbital electron decays back to its baseline energy.

Stimulated absorption: The process by which an orbital electron captures the energy of an colliding photon and is boosted to a higher energy orbital pattern.

Stimulated emission: An electron in a high-energy orbital will, if struck by an appropriate photon, emit a second photon of equal wavelength, phase, and direction to the original, colliding photon.

Tunable laser: A laser that can be adjusted to provide a selected output wavelength from a range of possibilities.

Ultraviolet: Electromagnetic radiation having wavelengths shorter than visible light, in the range between 0.01 and 0.38 μm.

YAG: A synthetic crystalline matrix composed of yttrium, aluminum, and garnet with a chemical formula of $Y_3Al_5O_{12}$.

Wavelength: The distance from peak to peak of a photon wave. The usual units for light waves are nanometers (nm) or micrometers (μm).

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The Origins of the Association of University Anesthesiologists

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Conceived in turbulent times but born in optimism at facing a brave new world, the Association of University Anesthetists (AUA, as it was called at its inception) is an interesting and important manifestation in medicine of the rapid intellectual and societal changes that were taking place in the United States in the immediate post-war (World War II) period. That this new organization was put together in a tumultuous environment is documented by the parting note of the first secretary, who was one of the eight founders of the Association, Austin Lamont. In 1957, he attached two interesting paragraphs to all of the correspondence that he had kept from those who worked to organize the group. On his presentation of the correspondence to the archives of the Wood Library and Museum in Chicago, Lamont wrote (1):

> This folder contains correspondence dealing with the formation of AUA and with the so-called Hingson Report. In both these matters strong personalities were involved. I believe the individuals concerned trusted my discretion, for they would write or tell me things they would not say to each other. There are, therefore, in this folder personal letters not intended for public view.
>
> But someday it may be of interest to a mature organization to look back on these matters. I think it would be a mistake to permit this folder to be opened until 1965 or 1970. By then the persons involved will have mellowed, the controversial issues will have been settled, and the personal references contained in many of their letters will no longer carry the sting they originally had.

Some consideration, however brief, of the environment in which the AUA first appeared as a structured force in academic anesthesiology is needed to understand the background information important to the story of this new organization's beginnings.

Academic Anesthesiology Before World War II

Before World War II, academic anesthesiology was characterized by many healthy accomplishments. The important academic presence in that era begins with and is centered around the first recognized academic department in the United States at the University of Wisconsin chaired and led by Ralph Waters. From the inception of the Wisconsin Department in 1927, Waters and his large coterie of distinguished followers, including E.A. Rovenstine who brought the academic message from the Midwest to the East at New York University and Bellevue Hospital, were engaged in studying the scientific bases of the important clinical problems of that era. Their skillful research in the anesthesiology of that period was a strong beginning. Equally important and interesting was the establishment and subsequent development of an academic arm, with respect to research and teaching at the Mayo Clinic under the leadership of the founder of anesthesiology in that institution, John Lundy. At the same time there were discrete and important burgeonings of interest in intellectual and other scientific matters that dealt with the anesthetic process. There were individuals who came from other disciplines like surgery, internal medicine, and pharmacology to study the biology of anesthetized humans with great foresight and clarity. Among these people was the young and able Henry K. Beecher who combined a scientific rearing with Professor Krogh in Copenhagen with clinical interest in anesthesia at the Massachusetts General Hospital. Beecher's book, *The Physiology of Anesthesia*, published in 1938, ranks among the landmark developments of the academic strength of anesthesiology. Despite these activities, there was insufficient time and opportunity to develop scientific researchers and teachers in anesthesiology, to say nothing of clinicians, in adequate numbers to have made a major mark upon all academic enterprises in the United States before the War.

The needs of World War II produced a rapid

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development of marginally educated physicians in anesthesiology to meet the critical exigencies of injury and disease resulting from massive warfare in all parts of the world.

The Academic Scene in Anesthesiology After World War II

At the end of World War II, the still young but seasoned veterans who had academic interests and talents saw these skills reinforced and greatly extended by the enormous clinical experience brought to them by the unfortunate results of institutionalized killing and wounding that is modern warfare. These young physicians in military anesthesiology were often, and in substantial numbers, attracted to a permanent career in this relatively new discipline; and, as was fortunately the case, a sufficiently strong cohort of this group opted for academic work. The education required for research and teaching careers was, for those days, rigorous. Today, in view of the enormously more complex problems to solve, the adequate clinical and scientific education of the immediate post-war era would be viewed charitably as evolutionary in character and accurately as floating on the margin given the problems to be resolved. Between the end of the war and the end of the decade of the forties, there was enough opportunity to accomplish the establishment of new independent departments of anesthesiology devoted to academic purposes of research, teaching, and complex patient care. There were enough individuals with investigative and educational talents devoting their entire career to academic pursuits to become a force mostly of youthful enthusiasm and of raw ability who wished to make anesthesiology the scientifically based discipline that it deserved to be. They worked hard to extend the benefits of those investigations to the care of patients who needed and deserved these attentions. There was a spirit of buoyancy, of powerful hope, and of great energy. There was also an important characteristic that marked many of the young leaders of the immediate post-war period. They had courage. Risk taking was known to be necessary and was entered upon with realistic reflections of the possible outcomes. Great success can be gained but equally great failure can ensue if the risk-taking results in an adverse outcome. In assessing his tenth anniversary as Columbia University's President, Michael Sovern quoted a favorite passage of his from William James on the subject of risk-taking (2):

> Not a victory is gained, not a deed of faithfulness is done, except upon a maybe; not a service, not a sally of generosity, not a scientific exploration or experiment or textbook, that may not be a mistake. It is only by risking our persons from one hour to another that we live all. And often enough our faith beforehand in an uncertified result is the only thing that makes the result come true.

There was ample evidence of the willingness to take the risks, because the past did not exist for most of the then young academicians in an important sense. Their future was one of brimming optimism, and their leaders were young, vigorous, and committed to a future boundless in scope. There was no possibility that the academic anesthesiologists of the immediate post-war period would be lulled into contentment with their present condition because of a good past. It simply did not exist in a serious way for them and, therefore, there were no weighty impediments to thinking ahead for the future.

This environment of optimism among a relatively small group of academicians had its counterpart among the clinical practitioners of anesthesiology but was differently arranged in priority and differently organized with respect to functions and goals. Practitioners in anesthesiology came back from the war finding a society in which their services were required far beyond the possibilities of numbers to satisfy. Young surgeons and others were deeply impressed by the contributions to patient welfare that could be provided by skillful clinical anesthesia. It is possibly because of the fact of short supply of competent anesthesiologists that an extreme position began to be noticed and apparently adopted as functional policy, if not official policy, by the controlling establishment in anesthesiology (although there were those who claimed it to be official). The practitioners of anesthesiology could use their new-found shortage of supply and high desirability as market forces to rectify the injustices of their economic oppression (as they viewed it) in the pre-war period by hospitals and similar institutions. An expression of these clinical market forces was a decision made to adopt a document known as the Hess Report of the American Medical Association (3) as policy. This report stated in part (chapter III, Article VI, Section 6):

Economic Bases Between Academic Anesthesiologists and Anesthesiologists In Private Practice

> A physician should not dispose of his professional attainments or services to any hospital, lay body, organization, group or individual, by whatever named called, or however organized, under terms or conditions which permit exploitation of the services of the physician for the financial profit of the agency concerned.

This section was interpreted by the officers of the American Society of Anesthesiologists (ASA) and the Directors of the American Board of Anesthesiology (ABA) in such a way that salaried forms of the practice of anesthesiology were deemed to be unethical. Attentive reading of the approved Hess Report does not support this interpretation so clearly.

Further on, the American Medical Association's (AMA's) House of Delegates report states under "additional guides," in teaching hospitals where there is research and education, that "the financial arrangements if any between the hospital and the physician properly may be placed on any mutually satisfactory basis" (3). Adjudication of conflicts, if needed, was recommended to be performed, where possible, on a local level.

Little recognition was given then or, for that matter, now about the dangerous irrelevancy of linking ethical behavior of a physician in practice to the manner in which he or she earned a living as a matter of principle. It is *how* these practice patterns are used that determines whether the method leads to inequities and to abuse of patient care rather than the process itself. Whatever the elements were, it was strongly believed by the University group that earning a living on a salary was the most agreeable arrangement to them at the time (despite dreadfully low salaries in many institutions). They behaved in this manner because there was a concomitant freedom from the necessities of schedules that impacted negatively on their time for scientific research and for education in favor of meeting the exigencies of a clinical schedule designed always by someone else and never under the control of anesthesiologists. Practitioners, who were vastly in the majority then and now, were of a different mind. They intended to retain the money that they believed they had properly earned, rather than have it distributed into the general coffers of a hospital or institution that may have profited by their efforts.

So intent were the practitioners of that period on enforcing this change that they attempted to require of every anesthesiologist who sought certification by the ABA that he or she be a member of the ASA and conform to the requirements of fee-for-service methods of earning a livelihood. The actual statement was that an applicant to the ABA must "be a member in good standing in the American Medical Association, the state and local county medical society or comparable national medical society approved by this Board. He (the applicant) must be a member in good standing of the American Society of Anesthesiologists, Inc." (4). This requirement was omitted in the booklet of information published on November 1, 1953, eliminating the matter that appeared to be of serious concern to university anesthesiologists. In fact, there never was secession from the ASA by the University group, although there were many problems between the practitioners' views and those of the academicians from 1950 until the AUA was organized in 1953.

The Gathering Storm

The matter achieved some considerable notoriety as well as serious concern on the part of academic anesthesiologist in that one of their number, a person of distinguished military performance in anesthesia during the war, as well as possessing a strong academic background in having come from the academic environment of the Mayo Clinic (Lloyd Mousel), was threatened with the loss of his Board certificate because he was working on a salary (5). There were other academicians who were prevented from joining the component societies of the ASA for similar reasons. One such example occurred in the component societies that comprised Maryland, Virginia, and the District of Columbia, in which an anesthesiologist from Johns Hopkins' Anesthesiology Division was refused membership in the component society and, therefore, the ASA for accepting a salary. The gathering storm was aggravated by extremists of the anesthesiology practitioner establishment of that period as well as by the excessive reactivity of some of the academic people.

An irony that is obvious, even to the passing observer, is the fact that the fee-for-service system modified by group practice features has actually prevailed even in most of the universities today, whereas it was viewed with dangerous alarm by the academicians at that earlier time. The current system, in turn, has led to other serious abuses in that instead of hospitals exploiting anesthesiologists, some anesthesiologists are now engaged in the dubious distinction of exploiting each other. The closed contract between the central power structure or the leadership of a group of anesthesiologists with an institution and the subsequent imposition of unfair and poor salaries on junior anesthesiologists (more common in private clinical practice than in academic organizations today) is the hallmark of how the human condition seems often to opt for base behavior given an opportunity of free choice. This observer recognizes that these comments are perhaps too cynical, a problem generated because one becomes attached to one's biases. As Alexander Pope, the distinguished 18th century poet, put it (6):

> To observations which ourselves we make
> We grow more partial for the observers sake.

These and other forces that molded the conception of the AUA and its ultimate delivery and birth are best understood by examining the correspondence that most of the featured players of the formative period had with and through Austin Lamont who functioned as a collecting center for a vast correspondence as well as, as he puts it, "the placing of confidences in him that would not otherwise be told." Lamont would probably feel some of those confidences should never have been breached. It seems to me that the story is better understood if both the actual statements of the players, where appropriate and useful, are studied at this time, some 38 years later, and are, to the degree possible, interpreted in the rather strong light of those turbulent times.

The Lamont File of Correspondence Leading to the Formation of the AUA

People of stern conviction are often afflicted with the inability to engage in a dialogue. At the time when they are neither talking nor writing, they are neither listening nor reading but simply waiting for the next opening to talk or write. This characteristic was true of all participants in an activity as fraught with controversy as was the genesis of the AUA. However, lest there be undue stress upon the fact that the AUA's beginnings were only the reaction to heavy-handed enforcement of a relatively archaic issue even then, i.e., the way one earns a living, it is essential to examine all the other issues and needs, especially the positive forces of university work, to understand how it all began. In the mind at least of this observer, there is little question that the AUA would have been organized sooner or later without the stimulus that was provided by the practitioner element in anesthesiology in insisting on a fee-for-service basis as one of the requirements of holding an ABA certificate. There was, after all, a modest-sized (compared to the present) but growing group of individuals interested and curious about the scientific underpinning of clinical anesthesiology. Many of them wished to have the opportunity to study important physiological and other functional changes in the human organism during the massive effects wrought by the powerful drugs and chemicals that are anesthetic agents. There was also a sufficiently strong group of people who were interested in imparting the knowledge that they or others had accumulated in a systematic way, i.e., teaching. They strove hard to improve the education of new people coming into the field of anesthesiology. These pressures were increasingly apparent and these aspirations were increasingly legitimate, as more and more people became interested in the science and education needed in anesthesiology.

Despite these positive and healthy factors, there is an opening salvo of anger in the Lamont correspondence by Henry K. Beecher. In due course, as will become evident, the formation of a group of friendly colleagues, at first groping their way to a solution of their common problems and later providing clear and powerful leadership for their goals, emerged from the mixture of conflict with external forces and the salutary responses to internal needs.

On November 17, 1950, Henry K. Beecher wrote to Austin Lamont at the University of Pennsylvania about his anger and discouragement about the pressures put against academic anesthesiology. Part of the emphasis of Beecher's interest and accomplishments is reflected in the title on this letterhead where he is self-characterized as the Dorr Professor of Research in Anaesthesia and Anaesthetist-in-Chief. Research is what the occupant of the Dorr Chair did in his work. After attending two meetings on anesthesiology (one in Miami Beach and one in Houston), he says to Lamont (5):

> It is perfectly clear that a tight little fascist dictatorship is being set up while the rest of us with any liberal views whatsoever stand idly and helplessly by.

Later on in the same letter, Beecher writes (5):

> Surely more important is the legislation designed to club all individuality into a mold. I find it impossible to believe that the ardent campaign against salaried individuals will not be turned against those in university positions when earlier battles are won, etc. etc.

Beecher concludes his letter by suggesting to Lamont that the latter lead a group in the form of a loyal opposition that could be made effective "in an organization to be called something like Association of University Anesthetists" (5). Beecher, thus inspired by the anger against what he believed to be philistinic behavior of the practitioner power structure, advocates a loyal opposition, but views it, perhaps paradoxically, to be expressed in the form of a new association that will become the AUA.

Some of the change in attitudes over the last 41 years toward academic anesthesiology may be seen in the change of title of Beecher's successor, Richard J. Kitz. The latter uses the title of Henry Isaiah Dorr Professor on his letterhead. Dr. Kitz views himself as the head of an enterprise that encompasses research, teaching, and patient care directly in the way his title is expressed. This larger view is a reflection of the change of the times. It is one of the successful stories of evolution probably aided by increased substantive recognition of the values of academic anesthesiology. The AUA played an important role in this transition from then to now throughout the country, symbolized by a letterhead change of title.

The Sense of Urgency Developing in Academic Anesthesiology

All of the Lamont correspondence reads, if one studies datelines, as though the correspondents sensed a high level of urgency to communicate. No time is allowed for lapse between letters. Lamont replies to Beecher on the November 21, 1950, 4 days after Beecher's letter was written, not counting time to be mailed and received. Lamont agrees with Beecher that the news of economic pressures on anesthesiologists in universities is deplorable. At the time of his first reply to Beecher, Lamont believes that all of the commotion is exaggerated and he does not, at first, think that an organization of university anesthetists would be necessary or wise. His views, of course, were to change rapidly in the next few months. In fact, Lamont's initial reaction was to say in effect that it was possible to satisfy the economic pushes of the power structure of the ASA by establishing what he called "partnerships in universities." It was an attempt to "window dress" (in his words) the salary question, which he later withdrew.

There appears to have been a lull in activity, judging from the Lamont correspondence, in that there are no further communications during 1950 and there are no letters amongst the principals, Beecher, Dripps, Lamont, and Papper in all of 1951. Clearly, there must have been some form of action during this interval of some 14 months, perhaps by telephone or conversations during medical meetings, as the resumption of the correspondence reflects that there was interim thinking about the problems of university anesthesiologists. My own files and notes and my recollections do not cast any further light or information upon this period during which no letters appeared in Lamont's files.

Letter writing was resumed with the letter of February 15, 1952 from Dripps to Papper in which Dripps proposes a modest model of the Society of University Surgeons for university anesthesiologists in which a small group of institutions could get together to discuss scientific research, either alone or in collaboration with basic scientists. He suggests a group consisting of Harvard, Columbia, Hopkins, Washington (St. Louis), and Pennsylvania as a beginning. He indicates that his thinking at that time was tentative and he would be happy and willing to have suggestions of other activities (7). In rapid reply, on the 19th of February, Papper's response to Dripps reflects his opinion that a larger group is a much better one for anesthesiology. He is strongly in favor of a group of academic anesthetists rather than one in association with surgeons. Papper comments about having seen Beecher just before this exchange of letters, and he also urges the establishment of a university group (8). The correspondence from this point on continues at a hectic pace and with unabated vigor. A principal advocate of a new association in some form is seen in a letter from Beecher on February 26, 1952, to Lamont (9):

> nevertheless my telephone continues to ring with discordant wails from all over the country. The most recent funny business has been going on at the University of Utah where apparently Scott Smith is involved on the side of union tactics.

He concludes his letter with being willing to form a travel group rather than a new society and to collaborate with others in opposition to the heavy-handed tactics he observes in the power structure of the ASA. Beecher's inclination, at that time, was to seek alliance with powerful groups in surgery whose views he thought would be most supportive of the positions and the needs of academic anesthesiologists against the heavy-handed "oppression" of private practitioners in anesthesiology. On Leap Year Day on 1952, Papper, in a short letter to Dripps, reaffirms his position in support of a larger, rather than a smaller, group for a new association, citing the real needs of a society to work on the mutual problems of research and teaching (10).

An Early Agenda for the Formation of the AUA Proposed by Beecher, Dripps, Lamont, and Papper

On March 3, 1952, Lamont writes to Beecher and presents to him an 11-point program in draft form with which he and Dripps are in agreement and for which Beecher's support is sought. Papper's views were also put forward as being in essential agreement with the major goals of our group of four (Beecher, Dripps, Lamont, and Papper) but repeating his desire to have a rapid evolution to a national organization. Lamont, in his letter of March 3, 1952, presents the proposals (11):

1. An organization composed of the anesthetists in some of the universities would be desirable.
2. Such an organization should start in a very small and informal way, perhaps as a travel group, as you (Beecher) suggest.
3. As a start, these might be included—Harvard, Columbia, Pennsylvania and two or three others who conduct effective research.

4. The primary purpose of such a group is the exchange of information regarding research.
5. For this reason membership in the group should be rather limited.
6. The consideration of other matters of interest (e.g. socio-economic relations, residencies, teaching, etc.) should have no place in the programs of the group's meetings. There is no reason, however, why the members of the group should not decide informally among themselves to stay over an extra day to discuss these matters if they wish. (This view was later abandoned.)
7. Should the members of the group eventually prove to be sympathetic and congenial and should the matters mentioned above in number 6 be still of moment at that time, consideration should then be given to enlarging the purposes of the group. (This view prevailed later.)
8. But, at least as regards socio-economic matters, it seems likely that any stand this group might adopt would be supported by a considerable number of anaesthetists (university or otherwise) who would not be eligible for membership in the group. (A reflection of the need to address real issues faced by all academicians.)
9. Consideration of these other matters and action upon them can at present be affected as we are now doing.
10. Formation of a group interested in research should not be postponed simply because there may be opposition.
11. As far as organizational matters are concerned, if such a group is formed, its first job should be to define carefully standards of eligibility for membership and procedures for election.

Clearly, Lamont's and Dripps' points of view emphasized the importance of small size of the group, a concentration of research activity, and an unwillingness to include teaching or other matters unless, later on, the group feels that attention should be given to them. There is, nonetheless, open-mindedness about the possibilities of including such matters as teaching and education, as well as considering what are lumped together as "socio-economic matters." As time goes on, the correspondence gets more and more crystallized toward what eventually became the AUA. Its initial interests in teaching and research were expanded to include items properly included under the aegis of university problems and issues.

One day later, on March 4, 1952, Dripps writes to Papper, still wanting a small research group rather than a larger group. He also advocates as much informality as possible and wishes to keep the organizational structure streamlined and simple, and the meetings relatively compact and short. He also impresses upon Papper his own need to be in Philadelphia and working with his Pennsylvania research program more closely. He says, therefore, he would be jealous of any time he would have to spend upon a much larger enterprise than the original thoughts of the small research group of interchange of experiences. He suggests, tactfully and parenthetically in a sermonette to Papper, that as the latter's responsibilities increase, he will face the same problems. He writes (12):

> I believe that as your responsibilities grow outside of your own department and university, you will appreciate why I take such a strong stand on this. As soon as you have to go to Washington for various committee meetings, leave the country on Army inspection tours and so forth, you will realize that additional meetings have got to offer you something, for you just will not have the time and energy to devote to them otherwise.

However, Dripps had a more open mind about the objectives of anesthesiologists concerned with research states when he says in the concluding paragraph of the same letter: "Perhaps you, Beecher, and I, plus a few others should meet during the Federation meetings in New York City and talk this whole problem over again" (12).

In keeping with the speed and developing force of the correspondence, Beecher responds to Lamont on March 7, 1952, about Lamont's and Dripps' memorandum of the statement of purposes. In a conciliatory opening paragraph, Beecher is very accommodating by agreeing to the approaches that Lamont and Dripps recommend to begin small and possibly enlarge later if things go well as Papper advocates. However, the short letter ends with anger. He says "I know anesthesia will suffer from the maneuvers of the unionists. All medicine too. It is a pity" (13).

Beecher's letter to Lamont of agreeing to think seriously about forming an association that would be small at first and then gradually grow also supports Papper's idea to include problems other than research, such as teaching, and "socio-economic matters" (not precisely defined nor limited).

There were lively discussions at meetings and by telephone among the various people who were members of, but not necessarily representative of their organizations, i.e., the American Society of Anesthesiologists, the American Board of Anesthesiology, and a group of active and vocal university people.

Some of the voices now being heard were new in the discussions over whether a university group needed its own organization to satisfy its important concerns about its activities and responsibilities. These individuals eventually were elected to AUA as "first rounders" in Boston in 1954.

Failure of Efforts at Conciliation Between the University and Practitioner Groups

In the autumn of 1952, Dripps wrote to Ralph T. Knight, the Chairman of the Department of Anesthesiology at the University of Minnesota and the then sitting President of the ASA, in an effort to improve relations between university and practitioner anesthesiologists. Dripps believed that it was a useful opportunity to clarify the needs of the University people and to persuade the ASA to address their grievances and concerns about being isolated from the mainstream establishment of anesthesiology. He, therefore, wrote directly to the President, who could have been very helpful as he was also a member of the university fraternity. It was a reasonable way to attempt reconciliation between the two groups.

Knight was an individual who had worked hard and conscientiously to establish modern anesthesiology at the University of Minnesota in an environment that was difficult for anesthesiology. However, it was an important institution as the surgical activities at Minnesota under the leadership of the distinguished Professor of Surgery, Owen Wangensteen, presented many opportunities for significant progress in both fields. There are those who, at the time, believed that the reason Knight was appointed Professor of Anesthesiology was because he would cause no undue commotion against a tough and strong leadership in surgery. Unfortunately, comfortable collegiate relationships between surgeons and anesthesiologists were still evolving at the time in some hospitals and medical schools. The role of the anesthesiologist as handmaiden had not yet died, nor was it replaced everywhere by mutual respect. Certainly, if one looks at Knight's contributions to academic anesthesiology, they belong to that transition period between the early significant academic contributors like Waters and his "offspring" Rovenstine and a few others and the new wave of strongly scientifically oriented academic anesthesiologists that was beginning to be evident after World War II. In short, Knight, while a university faculty member, thought and believed more like the mainstream establishment of practitioners in the ASA. Therefore, Dripps' representations to him were doomed to be unsuccessful, but they are summarized and considered here.

On October 3, 1952, Dripps wrote to Knight stating that he needed to put in a letter the points he wanted to make because he thought that he might be too busy in Philadelphia to be able to join him in a quiet face-to-face talk. He represented his views as being typical of a small group, not identifying the rest of us in his letter. The letter is, on the whole, conciliatory and recognizes the importance of economic and political justice for our specialty, which was the central concern of the ASA at the time. He then states that the ASA's preoccupation with economic matters precludes its interest in anesthesiological science. Dripps writes to the ASA President (14):

> We do not believe that the ASA is taking advantage of those individuals interested in and capable of attacking the scientific aspects of the specialty.

and further:

> In the past there have been abortive thoughts of an organization such as the Association of University Surgeons. In other words, we would form an Association of University Anesthesiologists. There is in such an organization danger of a real rift and I, for one, have not been willing to be too enthusiastic until other possibilities were explored.
>
> I wonder if it would not be possible for some of us to discuss this matter with the Executive Committee of the ASA in an attempt at working out a solution and in avoiding a head on collision? In my opinion the ASA will be better if it is strong in all phases of its activities, not just in some. I would appreciate your thoughts on this matter.

In keeping with the speed of reply by letter in those days, on October 10th (1 week after the date of Dripps' letter) Knight arranged an agenda position for Dripps and any others who wished to come to meet the ASA's Executive Committee in response to Dripps' request to do so. Knight then goes on in his letter to support and defend the position of the ASA, whose program, some 2–3 years old at the time, concentrates on economic matters to rescue physicians from the position of being economically "oppressed" by hospitals. This was said to be the motivation of anesthesiologists in the ASA to establish fee-for-service practice patterns among its members. Knight, while speaking of the emphasis on economic matters, also supports ASA's interest in science by writing: "This should not nurture, and I do not believe it has nurtured a lessened interest in scientific development" (15). He says that the ASA meeting should have something for everybody in the membership and that means diversity of program. Knight does not oppose the establishment of an organization for academicians and he writes in the same letter to Dripps (15):

> It is certainly understandable that University Anesthesiologists might want to have meetings or an organization of their own. I do not think it would be detrimental to our society to do so and I do not think it would cause any rift. I do, however, believe it would be much better if their programs were within or continuous with the ASA meetings so that the whole membership could have the benefit of listening and learning.

This conciliatory message seemed to state that the practitioner establishment wanted to continue to have university people in ASA's programs or, if that was not reasonable and in the best interest of university scientific development, they (ASA) could accept a separate organization. There was hope for improved relationships and tolerance with healthy mutual understanding. The quarrel between university academicians and clinical practitioners in anesthesiology, therefore, seemed to have been peacefully and comfortably resolved without further ado. Such, however, was not to be the case. The meeting between Dripps (and others he might invite) and Knight with the Executive Committee of the ASA was postponed because Dripps left for Korea on October 30th to conduct field studies of plasma expanders for the Surgeon General of the Army of the United States during the Korean War. No substitute date was suggested for Dripps to meet with the ASA's Executive Committee, and that meeting evidently never took place. I do not recall being invited to such a meeting nor attending it.

Not long after this cordial exchange of letters, conflict seemed to have been rekindled by events that suggested that the ASA's position was going to remain tough despite the apparently conciliatory views of its President. Beecher, on November 17, 1952, in a letter to Lamont, discusses the matter of Georgetown University in Washington, D.C., where the ASA took a position declaring that the members of that Department were "unethical" because they worked for a salary. Beecher was considerably exercised about that incident and viewed it as serious. For the first time, there was some disagreement among the original group of four about the importance of an external matter. Beecher writes (16):

> I went to New York for the express purpose of seeing Papper. I was dismayed to hear him say that he did not think the matter was very important, at least as far as Georgetown was concerned. That matter was and is important to me because it was the first time the unionists had attacked a university hospital which had had the salary system. You will recall that they had said that they would not do this.

Beecher then proceeds to state that there has been a return of agreement among the original four, in the light of further discussions, and he writes to Lamont: "I am extremely pleased that Papper believes that these matters are important and he is, as I understand it, eager to do something about them" (16). Beecher then reiterates the need for a separate university organization once again and urges that Papper and Dripps come to some agreement about their present differences of view with respect to the size of the prospective organization. Dripps favored a smaller organization and Papper, a larger one. In the same letter, Beecher sought outside support for the position of the university anesthesiologists from a strong figure in academic surgery and from the AMA. He describes his activities (16):

> Because I thought the matter was so urgent and because nothing else seemed to be happening, I wrote a letter to a surgical friend of mine (Evarts Graham). He was much agitated and took the matter up with the Board of Regents of the American College of Surgeons, with the American Surgical Association and with Donald Anderson of the American Medical Association. . . . The end result of this is that we have a strong body of support in other quarters of medicine.

Beecher furnished Lamont with a copy of the letter that he had written to Dr. Graham, which describes in part the great concern that Beecher had about how things were going with respect to viewing a salary position as being unethical and, therefore, not acceptable to the establishment in anesthesiology. In a letter that is undated but presumably was written in the autumn of 1952, he writes (17):

> A good many prominent anesthetists have decided that it is unwise for any man to accept a salary "from a lay corporation", i.e. a hospital or a university. They are busily imposing this curious point of view. Their chief weapon is a threat that the young man will never be certified by the Board if he takes a salaried position. These anesthetists have said they had no intention of altering university arrangements already in effect. Frankly, I never believed this statement. Proof is now at hand that it was not sincere.

The Role of Distinguished Surgeons and the AMA

Beecher's very strong efforts to seek outside help from people prominent in medicine and surgery resulted in the agreement by distinguished surgeons to support the university anesthesiologists' positions. There was also a conciliatory letter to Beecher from Dr. Donald Anderson, then the Secretary of the Council of Medical Education and Hospitals of the AMA, that the Council and the ABA were in agreement that there can be no economic pressure on the Board's Diplomates relating to the issue of salary vs. fee-for-service practices.

In a letter dated October 13, 1952, Anderson wrote to Beecher (18):

> The Council made it clear that it would not tolerate being a party even indirectly to such activities (i.e. economic pressures). The representatives of the American Board stated that the Board had not been a

> party to such activities and viewed them in the same light as did the Council.

A joint statement from the Council and the Board was subsequently issued to this effect.

Four days later, on October 17, 1952, Beecher replied to Anderson. Beecher, in effect, stated that he did not doubt the position of the Board officially nor that of the AMA Council, but he maintained that individuals in the power structure of political anesthesiology were using their Board Directorate positions to undermine the joint statement. He states his disbelief in the efficacy of the joint statement in this fashion (19):

> I do have reason to believe that men who are active in the politics of the Board and of the American Society of Anesthesiologist have been responsible for threats being made that certain individuals would not be certified by the Board if they took salaried positions. . . . I do not believe it or any such statement will get to the root of this serious problem. It might help if the Board members were asked to sign the statement as applying not only to joint Board action but as representative of their own beliefs. I strongly suggest that this be done.

It is interesting that the Hess Report, which was the foundation document of the ASA establishment's economic pressures, was not in the opinion of Anderson, the document that ASA alleged it to be. In a letter to Beecher on October 24, 1952, Anderson says (20):

> The history of the Hess Report is a long and confusing one. Perhaps I can best sum it up by saying that three or four years ago certain specialty groups endeavored to stampede the American Medical Association into enforcing certain rigid economic practices favored by these groups. From the start the issue was hotly debated with the more mature and responsible leaders of the AMA opposing this move.
>
> At one stage, a version of the Hess Report was adopted which did place the AMA in such a position. However, no action was taken by the AMA to implement this feature of the report. Rather the responsible leaders of the AMA worked diligently for the adoption of a new version of the report which would not put the AMA in the position of enforcing economic practices. This new version, a copy of which is enclosed, was adopted in 1951 and I believe will stand as the AMA's policy in the relationships of hospitals and physicians. (No copy was found in the Lamont files. A copy of the 1950 action of the AMA on the Hess Report was supplied by Dr. James Todd, the current Executive Vice President of the AMA.)
>
> I think you will agree that the report in its present form does not in anyway justify those who would disrupt university departments, although it is possible that there may be individuals or groups who are attempting to misinterpret the report to further their own ends.

The Discussion With the AMA

At the conclusion of this exchange of letters between Anderson and Beecher, the latter almost in the finality of discouragement does not accept Anderson's views even though he understands that Anderson did the best he could. He writes to Anderson (21):

> I would be less than honest if I led you to believe that I thought it would accomplish a single thing. I know the men on the Board very well indeed and I cannot believe that a single one of them will be deterred in their individual actions by this joint statement. However, please do not construe this letter as harshly critical. I know that these problems are complex and I do not doubt that you are doing the very best that you can to solve them.

That is where the conflict over salaries and fee-for-service practice stood on October 29, 1952.

At the end of this period of exchange of letters between Beecher and Anderson, which resulted in any uneasy impasse, Lamont collected a summary of current views from Beecher, Papper, and perhaps others whose names are not mentioned to provide a memorandum for Dripps who was still in Korea with the Army.

In the memorandum that Lamont prepared for Dripps on November 17, 1952, he described the joint statement by the AMA Council on Medical Education and Hospitals and of the American Board of Anesthesiology. Among the points mentioned in a reading of the joint statement by Roland Whitacre (an ABA Director) were (22):

> The Council and the Board consider the matter of the financial arrangement that may exist between the hospital and its anesthesiology staff one that is not within their proper purview, provided the relationship between hospital and physician conforms to the policies and the Principles of Medical Ethics of the American Medical Association.

It was on this statement that the issues of conflict were to be drawn, as many in the university group, Beecher most emphatically, neither trusted nor accepted the integrity of the commitments made in the joint statement. Our group of four continued to receive evidence that salaried practice was unacceptable to the ASA power structure. In his memorandum to Dripps, Lamont states that Whitacre affirmed the fact, in response to a question posed to him, that if an anesthesiology staff is not in conformity with the principles of the Hess Report its residency would be disapproved. Whitacre's reply was inflammatory under the circumstances, and thus began the heat of conflict once again. In the memorandum for Dripps, Lamont describes the negotiations that Papper had been carrying on with Drs. B. B. Sankey and R. Whitacre of Cleveland, Ralph Knight of Minneapolis, and others with respect to the position of university departments. Lamont says (22):

> He (Papper) thought he was making good progress towards an arrangement that would satisfy everyone, and he had made plans to have Sankey meet in December or June with a number of representatives of university departments. These conversations had been continued up until twelve hours before Whitacre's statements to the Delegates. Papper was therefore very surprised and upset by W's (Whitacre) statement. He is sure that W knew of his conversations with Sankey because the two are very close professionally and socially (their wives are sisters).

Lamont proceeds to summarize the views of those present. He writes (22):

> Papper now feels that the university people should get together to discuss the matter. . . . He feels that whatever we do should be perfectly open and that probably a larger group would be better than a smaller one. . . .
>
> Beecher, as you know, has been convinced for some time that these men (Whitacre et al.) are determined to do as much mischief to the specialty as they can. He thinks we should get together to discuss the matter and he also believes we should get on with forming of a group of university people, as I have suggested under A. below.

The Decision Is Firmly Made to Establish the AUA

In summarizing all of these discussions and the status quo for Dripps, Lamont writes (22):

> A. We would proceed forthwith to organize a small group of university anaesthetists (and please let's not call them University Anaesthesiologists!) which will meet at least once a year to present papers and to discuss research projects in progress. These would be closed meetings.
>
> Either just before or just after each meeting the heads of departments who wish to do so could meet to discuss administrative and other matters of interest to them.
>
> B. . . . Another principle is that a private organization like the Board should not have such power as it apparently seeks, to interfere with and to exercise coercion in regard to those aspects of our life which we Americans have always held to be our own business so long as we obey the law of the land.

Under Item C of the memorandum, Lamont believes that we should set up our own certifying examinations under joint university auspices if the Board takes steps to approve the residencies in anesthesiology. He even perhaps somewhat wistfully adds if all else fails we should seek external help.

> Perhaps we could join with the surgeons in certifying anaesthetists (22).

The Lamont memorandum concludes, finally, with a behavior pattern recommended to university people in forming the new association (22):

> C. Because the university people tend to be more individualistic and because we probably each have our own idea of the proper path for the specialty, it would not surprise me to find considerable areas of disagreement among us (evidently still present!) in so far as we can we must assume that everyone of us is acting solely with the good of the specialty in mind. We must try to look at the matter in the round and not just from the view point of our individual situations. . . . This is not a matter of ethics nor of religion, but rather something that history has proved many times. By giving up ourselves to something greater than our selves, we ourselves become something greater.

Lamont cannot resist his return to earth in a slightly self-mocking deprecation of his lofty principles as he says (22):

> When I hear my grandfather talking I know it is time to stop.

The next day, on the 18th of November, Lamont resumes his correspondence with Beecher and gently reproves the latter for his excessive vehemence and perhaps his impulsiveness. He writes (23):

> I think we must be very cautious about making charges we cannot prove. I haven't heard recently of any threats, though I knew of at least one in this city some years ago that I could prove. If we hear rumors of threats let's try by every means to track them down and get the facts, preferably in writing.

Two days later, on November 20, 1952, Lamont, in another letter to Beecher, provides him with a small list of suggested people for membership in the new association. Unfortunately, the actual list was lost and it cannot be determined who Lamont may have had in mind for initial membership beyond the group of four then working on the problems of university activities.

Evidently, the problems were becoming more widely known. It is certain that Dripps and Lamont discussed these matters with their colleagues in the Pennsylvania Department. On November 21, 1952, in a letter to Lamont, Eckenhoff, then a senior colleague of Dripps' at the University of Pennsylvania, advocates the formation of a small informal group consisting of the departments of anesthesiology at Harvard, Columbia, and Pennsylvania to meet without any formal structure. The activity he thought should be entirely research oriented and informality should be the keynote of the pattern of the meetings. Eckenhoff valued the plan of informality in dealing with research matters, but also felt that this structure would minimize, if not eliminate, objections by others to the activities of the university groups mentioned (24). On December 1, 1952, after receiving Lamont's memorandum of the points made by Eckenhoff, Papper agreed to the idea of informality of the organization at its beginning, consisting of the three institutional departments that were recommended by Eckenhoff. He goes on to describe his vision of a larger organization by writing (25):

> However, I have been among those who felt that a larger group of people interested in research in anesthesiology was desirable. I believe that Bob (Dripps) and Harry (Beecher) are not in accord with this thought for reasons we have all discussed previously. However since a beginning must be made somewhere, I would like to go along with your thought that we meet in Philadelphia on April 3rd from just the three departments, to discuss at large among other things, what form such a group should take. I should like to consider that an open question at the present time.

Papper's reluctance to go along with the informal, small group began, in a short time, to be shared by others as events began to mount in frequency and intensity. On December 10, 1952, Lamont prepared a memorandum report of conversations and correspondence for the Pennsylvania Department. His opinions of the issues at the time are illustrated by a few excerpts from his report. The quotations illustrate not only the intensity of feelings at the time, but the fact that individuals of the original group of four, otherwise thought to be strong and determined and even stubborn in their views, show evidences of accepting the need for change with the evolution of events. There is also a clear reflection of some of the volatility and instability of the times in that these otherwise determined individuals seemed to be movable occasionally from previously fixed positions. Lamont, among other statements made to the Pennsylvania Department, says (26):

> Papper thought a small group might be open to charges of snootiness, oligarchy, etc. But he will go along with (the) small group idea to see how it works.

Lamont, in relating these relationships to the other organizations in anesthesiology, writes (26):

> Papper emphasized that the only long term solution of our problem within the existing frame work lies in our seeing to it that men of high standards are elected to the Board and to office in the ASA. . . . It will take a lot of work and results will be slow in appearing. Papper is unwilling to consider any solution that lies outside the existing framework.

Papper's attitude apparently changed several times and appeared to be one of vacillation between accepting the established framework and rejecting it. This indecision evidently was a reflection of his uncertainty of the time, as to whether the long-term benefits accruing to academic anesthesiology would best be served in a separate organization or within the existing establishment. Papper may have responded to the ironic observation of Jacques Barzun who was and is his mentor and close friend (27):

> . . . The simplest way to stop the transacting of business and split the ranks is to appeal to a principle.

He might also have been persuaded by the comment of Oscar Wilde in retrospect (28):

> Experience is a name everyone gives to their mistakes.

Were we doing something unproductive in our obsessions with the hostile forces of the ASA? There was little doubt as events unfolded by the end of 1952 that the best course for university development in anesthesiology in the post World War II period was to establish an independent organization. Beecher's view in the Lamont memorandum of December 10, 1952, although stated with excessive force, was one that was quite appropriate to the events of the time. Lamont cites Beecher as follows (26):

> Beecher would like us to be a band of brothers sworn to find the solution even if it is meant going outside the existing framework.

In terms of self-reliance, the principles important to a society that had become entrepreneurial were also relevant to the now evolving new organization (26):

> Beecher and Papper felt that we should not seek support outside the specialty unless it becomes evident that we cannot make real progress on our own.

The Rapid Gathering of Support Among University Anesthesiologists for the Formation of the AUA

This is a change of view for Beecher in view of his previous seeking of support from powerful individuals in the field of surgery.

As the correspondence was beginning to crystallize more definitely on the need for a separate association with other questions being left open for further consideration, there existed, almost simultaneously, a similar but not very vocal group of younger people in anesthesiology who were thinking also that they had need of each other professionally and perhaps personally as well. Harmel, on December 23, 1952, wrote to Lamont (who was one of his close friends and former mentor at Hopkins) that some of the discussions in our group of four, whom he termed "Old Turks" had become known to the anesthesiologists on the Board of Directors of the New York State Society of Anesthesiologists. Dr. Harmel, who, at that time, was Chairman of the Department of Anesthesiology at Downstate Medical Center in New York City, reflects on the possibility that there may be a split between the university group of anesthesiologists and the larger numbers in the specialty who are engaged in private practice. He does not seem overly concerned about any risks that may be involved. He believes that some of the problems we are seeing in academic anesthesiology are part of the problems of the world at large. He thinks (29):

> The cloister of the University is invaded and I think we must prepare, in some manner, to open our doors to new ideas, new approaches and an interchange of ideas which goes beyond the jealous guarding of secrets. Therefore, I think that this small movement amongst the "Young Turks" (Harmel and Artusio among others) to exchange ideas and confidences concerning the work and teaching is significant. It is a step toward the establishment of a University idea which goes beyond the archways of the campus.

These groups of Old Turks and Young Turks were to become unified without any difficulty in the Association of University Anesthetists that was now destined to emerge in a matter of months.

After the Christmas Holidays and the settling into the new year of 1953, Lamont's files of correspondence take on a cast in which it seems more and more obvious that the conversations between the practitioner establishment in anesthesiology and the university groups were to be fruitless in achieving a compromise. It began to look as though Walter Gropius may have had us in mind in examining both groups when he said (30):

> Specialists are people who always repeat the same mistakes.

Possibly, even John Kenneth Galbraith was thinking of people like us, although he addressed a more universal phenomenon when he wrote (31):

> Meetings are indispensable when you don't want to do anything.

Beecher, in his letter of January 22, 1953, to Lamont reflects the impasse with respect to reaching an accommodation with ASA and ABA officials. He writes (32):

> I thought this was a terribly depressing conference (with ABA Directors in Cleveland). I could not see that a single thing was accomplished in three hours in any constructive way. I came away with a heavy conviction that the only reason "they" consented to meet with us is because they believed they could "explain" the situation to us so that we would embrace their point of view and stop being so troublesome.

He concludes (32):

> I should think we had better proceed quietly and straightforwardly with the plans for the university anesthetists.

The decision to establish the AUA was, therefore, all but completed. There was no longer a possibility of finding a compromise approach to furthering the needs and interests of university anesthesiologists with respect to their practitioner colleagues.

The emerging pattern of increasing firmness among the group about the need to form AUA because of the external pressures that were highly negative and were imposed by the practitioners in anesthesiology is reflected in a letter of March 2, 1953, from Dripps to Papper. He writes (33):

> I suggest that we form a Society of University Anesthetists, as we have all been discussing and believe that we should form it at once.

The Problem of Selecting Charter Members for the AUA

Dripps was a person of firm convictions and often appeared to possess black-and-white views of issues and people—a quality that was very appealing to me and to many others, but sometimes could be disconcerting. In that letter from Dripps to Papper he is very specific about people that should *not* be invited and others that should. As the correspondence is open to anyone who chooses to read it, those individuals that care to study Dripps' opinions about people are urged to have a look at this letter. He thought that the creation of the AUA would see widespread receptivity in most of the then departments or divisions of anesthesiology at universities, and he named some specifically. On the negative side, Dripps suggests that because of the hostile leadership in those institutions it is pointless to expect favorable replies from the Departments at Utah, Iowa, Oregon, Minnesota, and Hahnemann. Dripps does not expand on his reason for noting the expectation of refusal by some, and he also states that he does not believe that they should be invited in any case. Some of the opponents to the idea of the AUA were to be found in those institutions; but at least in two instances, Dripps' views were possibly personal rather than professional. Those were in Iowa led by Dr. Stuart Cullen and in Oregon whose chairman was Dr. Frederick Haugen. There is nothing further in the correspondence that explains Dripps' attitude about those two institutions. My own recollections cast no further light on the subject. In point of fact, as will be seen, Cullen and Haugen attended the meeting of the first round of elected members and were always supportive of the AUA from the beginning (33).

Dripps also, in the same letter to Papper, drafts a proposed letter to those who will be invited to join in the first round. The AUA's purpose is now clearly articulated as events became more and more definite in the march toward association formation. The draft letter proposes in part (33):

> A number of us in university departments of anesthesia have decided to form an organization concerned with problems of particular interest to individuals in academic life. We believe that members of such departments differ from other organized groups of anesthetists since in addition to caring for patients, they must evaluate teaching techniques, teaching facilities and foster sound programs of research. The development and financing of their complete program also poses unique problems.

It was now becoming apparent as the discussions pushed forward that the original purpose of small size and collegial informality, concentrating only on research, was gradually enlarging and taking the form that deals with an entire academically oriented constituency. Papper's reply, almost by return mail, to Dripps supports the position of setting a first date for a meeting and hoping that he, Beecher, Lamont, and Dripps will be able to agree at once on the initial steps. First soundings were made of individuals like Drs. E. A. Rovenstine and Joseph Artusio in New York and Drs. Benjamin Etsten and Julia Arrowood in Boston whether they would join in support of the idea of establishing an association. By March 20, 1953, things had progressed even more rapidly and a proposed constitution modeled on that of the Society of University Surgeons was put together by Lamont, plus a tentative list of possible future members and also a suggestion to enlarge the founding membership to eight. It was decided to get things prepared as rapidly as possible and, as Lamont puts it to the other members of the group of four in his letter of March 20, 1953 to Beecher with copies to Dripps and Papper (34):

> Since Papper thinks that an announcement before the AMA meeting in June would have a vulnerable psychological effect, could we not make such an announcement for the larger group in time for the June meeting if we were to write fairly soon to most of the members of the larger group, enclosing a copy of the constitution and asking each whether he would accept membership if he were elected. In this way we could send out notices of announcement immediately after the meeting May 9th.

The Group of Founders Is Expanded to Eight

There is no indication in the correspondence as to how the decision was made to increase the original group of four of Beecher, Dripps, Lamont, and Papper to eight by adding Etsten, Faulconer, Orth, and Robbins. Each of them was evidently contacted by Lamont and agreed with alacrity to serve as founding members of the newly created Association. They were the group that was to meet in Philadelphia on May 9th to formulate some of the basic issues to be presented at the meeting of invited members, which was to be the second official meeting of the AUA and was scheduled to take place in Boston in early 1954. The composition of the letter to those to be invited to attend the first meeting after the founders' meeting in Philadelphia was the subject of some discussion among the original group of four. For instance, in the letter of March 26, 1953, from Papper to Lamont, Papper urges the elimination of the words that characterize the original group as belonging to what Lamont called "the Eastern Seaboard." He prefers a national structure (35):

> We (or at least I) want the first flavor to be intellectual, but also *national*.

This was another effort to push toward a national scope for the new Association. The idea had by now become acceptable to the founders and to the first elected group.

On March 26, 1953, the die was definitely cast to establish the new Association. In a letter from Lamont on behalf of the original group of four in which he signs himself Secretary Pro Tem, Association of University Anaesthetists, he writes to Faulconer, Etsten, Orth, and Robbins describing the establishment of an association of university anesthetists and invites each of them to become one of the founding members now enlarged to eight in number. The broadening of the founding group to include at least one southerner, one additional northeasterner, and two midwesterners was believed at the time to be symbolic of national involvement as well as the need to deal with our own peculiar and important problems more effectively. Lamont says in part (36):

> What we need is an opportunity to present current and contemplated research projects in an informal (or formal) manner and to subject them to intimate, informed, friendly, and constructive criticism and discussion. We believe that a meeting of university anaesthetists would prove to be much better suited to our needs than anything now available.

Lamont now also supports the activities beyond research alone and indicates (36):

> We also consider that such a group might be helpful in improving methods of teaching and in solving problems of organization in university departments and of their relations to the university as a whole.

A copy of the proposed constitution was also enclosed with his letter of invitation to the additional four founding members who were to meet in Philadelphia in May. As a cordial and pleasant added touch to the invitation, Lamont invited each of the four to stay at his beautiful home rather than at a hotel. All four accepted promptly within a week's time of the invitation and the founding membership was then established. A list of prospective "first-round" members was also sent to each of the four. The number consisted of 55 names, including two individuals from the United Kingdom (Mushin and Pask) and one Dane (Mörch). The origin of the 55-name list is unclear at this time. It may have been a collection of all the names submitted by the original group of four or it may have been compiled by Lamont and Dripps. In the absence of more definite information and as it differs rather sharply in both directions (i.e., some on Lamont's list were not elected and others not on the list were elected), it is best simply to speculate that the results of sending out a list to the additional group of four may have been the stimulus that settled on the list that was finally formulated. Another inconsistency in the correspondence is the fact that in all of Lamont's letters to the group of four and to others, he consistently refers to a group of 26 names suggested to be first-round members and not 55. The group of 26, one can only imagine, must have been the result of the deliberations either at the May meeting of the founding group or in another manner not apparent in the correspondence collected by Lamont.

Acceptance of Membership by Charter Members Is Rapid and Enthusiastic

Letters of acceptance of election by "first-rounders" were all dated prior to the time of the May meeting of the founding group. The acceptance of election was prompt, enthusiastic, and almost 100%. One must, therefore, conclude that the final list of the 26 had been agreed upon before the May meeting of the founding group. Whether the second group of four of the founders had any voice in it is impossible to determine with certainty. Knowing the individuals and the degree that memory is not totally faulty, my opinion is that they must have had input into the choosing of the 26 additional names to be added to the eight founders. Most of the replies were characterized by the enthusiasm and support expressed by Artusio in his letter of acceptance to Lamont dated April 13, 1953. He says in part (37):

> I wholeheartedly agree and am one hundred percent behind the formation of a group of university anesthetists. I wish to signify my willingness, without reservation, to accept election if I am elected.

Some of the letters, although almost always enthusiastic, raised a few questions of substance and some of detail. There was an interest on the part of Stephen, for example, to explore further whether there should be affiliation with the ASA in some form. Stephen, like the others, was not as yet informed of all the discussions that had already taken place with the ASA officers and with the ABA Directors. Others, like Virtue, raised some questions about the details of the Constitution that were validly helpful. These suggestions were accepted by Lamont and incorporated into the official documents. Still other suggestions were typified by those of Adriani who suggested an age limit of 45 or at most 50 to be sure that bright young people doing active research would always be in control of the AUA's meetings. It is interesting to note that this issue of age, fixed numbers, and the idea of preserving the youthful vigor of the membership has always been present for consideration, even before the AUA's actual formation. The problem, if it is a problem, has not gone away and probably never will. A few of the first group may not have sent letters to Lamont, and at least two interpretations are possible. It is conceivable that some letters were lost or not deemed to be important. It is also possible that acceptance was accomplished by telephone or in person without notations for the record. I suppose a third alternative may exist. Two or three of the more dubious and conservative first-round members were not sure that they wanted to be elected until they had a look at what the first meeting was like. Whatever the explanation of a few missing letters of acceptance is, all of the first-round invitees accepted membership, were supportive from the outset, and appeared at the Boston meeting in 1954.

After the receipt of letters of acceptance from the invitees, the original four were asked by Lamont to react to those letters that presented suggestions or other views. Beecher's views, on April 21, 1953, in his response to the material sent by Lamont to the three of us, can be summarized by wholehearted support for the new venture, but he is consistently extreme in the statement of his position. He writes (38):

> I think it would be disastrous for our little group to be affiliated in any way with the ASA. We are not in competition with the ASA and, in fact, are probably everyone of us members of the ASA. It seems to me that any official affiliation with the ASA would promptly nullify any prospect of us rescuing the anesthetist from the political and financial morass which threatens to engulf him, at least to separate him from all others in medicine.

Even before the Philadelphia meeting of the eight founding members, knowing that the organization would be a success or believing it would be from the start, Beecher, in a letter of April 21, 1953, to Lamont, invites the Association to meet at Harvard in 1954, at a date to be arranged, for a scientific and business meeting. The meeting of the founders group in May of 1953 in Philadelphia was to be entirely business and no scientific papers at all were to be presented. At about the same time, in a letter of April 23, 1953, from Rovenstine to Lamont, the former happily accepts membership in the AUA and makes two strong suggestions for its activities. In addition to research, he stresses the importance of teaching and educational activities for the new AUA—an activity that he always found congenial and important to his own mission. He also warned against domination by an inner small group of powerful people that could detract from the scientific value of the meetings. He also felt that social activities, incidental to the meeting, should be minimal. April 23rd seemed to be a day of letter writing for the group of four and Papper, in a letter to Lamont on that same date, seems to waffle temporarily from a previously consistent position with respect to the issue of affiliation with the ASA. He says in part (39):

> I wrote just yesterday that I thought the Association of University Anesthetists ought to be an independent organization. However, I suppose we should consider seriously affiliation within the ASA providing the things we wish to accomplish will be officially accepted policy. That is to say the goals we attempted to accomplish in Cleveland might possibly be accomplished in the manner Stephen suggests.

He makes further suggestions that membership in the ASA should not be required for Board certification and similar provisions, and concludes by saying (39):

> If these positions were accepted by the ASA I would have no objection to affiliating our association with the national society.

Evidently on further reflection, thinking that these suggestions were ones of weakness rather than of conviction, he writes in a hand-written postscript to the same letter (39):

> These are rambling thoughts—conditioned by the first sunny day in NY in a long time. I'd like to think more about.

He did think more about these matters subsequently and returned to his original more tenable position that the AUA needed to be an independent organization.

The Question of Age Limit Surfaces Early

The age limit was addressed by Beecher in his comment to Lamont on April 28, 1953. Beecher objects to Adriani's position about retiring to senior status or some similar academic heaven despite his obvious conflict of interest, as Beecher was 49 years old at the time of his writing. He stated that anesthesiologists do not have a comfortable place to retire to like surgeons do, which for them is the American Surgical Association. He concludes by stating (40):

> I think we ought to look very sharply at this question (age limitation) before we make any easy assumptions that the group ought to be kept young, vigorous, etc. etc.

Apparently, on a less sunny day in New York or the firm establishment of springtime in that city, Papper got over his indecision about the independent structure of the AUA and in a letter of April 29, 1953, to Lamont, he writes (41):

> I am delighted that everybody feels that we should not tie the new association in with the ASA. My second letter on that subject was written in a bloom of

> optimism. I know full well the ASA will not make the two concessions that I felt were a prerequisite to the Association being affiliated with the ASA.

Quiet optimism then prevailed in Papper's mind as he concluded his letter by saying (41):

> We should have a pleasant future ahead for all of us.

For those readers interested in some of the specific details of the correspondence among the founding members and the group of first-rounders, on the 30th of April, Lamont summarizes all of the points that were raised in the exchange of information about the formation of the AUA by using a combination of excerpts from letters and notes from his own files. As these main points have already been summarized in this essay, it is suggested that further detailed information, if desired by the reader, be sought from the Lamont file. Lamont's summary of all the material was not only useful to the original group of four but was especially useful in briefing the second group of four, now firmly established as the founding members of the AUA, and eventually the group of 26 elected on the first round.

The AUA's First Meeting in Philadelphia Is Organizational and Attended Only by the Founding Group of Eight

On May 9, 1953, the Philadelphia meeting of the founding members took place. All were present except for Orth who could not attend at the last minute, but he sent his views by letter. The Constitution and By-laws were discussed and appropriate suggestions for change were made. Lamont states in his notes of the meeting (42):

> It is fair to say that no substantial changes were made, that the changes were in the direction of greater precision and simplicity.

The minutes of that meeting included the names of the first 37 members (including the original group of four and the recently established founding membership of eight). They were Adriani, Allen, Apgar, Arrowood, Artusio, Beecher, Brewster, Bunker, Converse, Cullen, Van Deming, Dripps, Eastwood, Eckenhoff, Etsten, Faulconer, Greene, Greifenstein, Hampton, Harmel, Haugen, Holaday, Keats, Lamont, Landmesser, Morris, Orth, Papper, Pender, Proctor, Robbins, Rovenstine, Stephen, Van Bergen, Vandam, Virtue, and Volpitto.

The AUA Consists of All University Leaders in Academic Anesthesiology: The Second Meeting Including All Charter Members Is Held in Boston in 1954

The second meeting of the AUA was scheduled to take place on January 16, 1954, at the Massachusetts General Hospital in the Ether Dome. The founding group of eight appointed themselves as Executive Council under the new Constitution until the Boston meeting. Lamont was appointed Secretary Pro-Tem also until that meeting. The first group of officers were, therefore, to be elected in Boston.

This meeting took place on January 9, 1954, at the Massachusetts General Hospital. It was chaired by Beecher and consisted of two groups of laboratory studies that were very well received and the first major presentation of the important subject of measurement of subjective and pain-related responses to come from Beecher's Department and Laboratories. The evaluations of hypnotic power, the placebo response, and the relative and comparative actions of analgesic substances, especially the narcotics, were presented in a group of most interesting papers. There are no notes available on the nature of the business meeting in detail except that officers were elected.

The first Council consisted of E.M. Papper, President; Austin Lamont, Secretary; James Eckenhoff, Treasurer; and the Councilmen-at-Large were Stuart C. Cullen, C. Ronald Stephen, and Frederick Van Bergen. The 1955 meeting was scheduled to take place at Duke University on the invitation of Stephen. Those were the facts that brought to a happy and successful conclusion the struggles of the formative period of the AUA.

Epilogue

What does not appear in the Lamont file were the serious reservations of a few of the influential people in academic anesthesiology. Their views were to determine whether the infant AUA was to be a national organization representative of the academic community or whether it would become, in effect, a pleasant and regionally dominated social club of, to use Lamont's characterization, the "Eastern Seaboard." Their reservations were earnest and serious, and they had to do with being sure that the AUA's positive purposes far outweighed in importance the negative pressure thrusts that stimulated its organization. It was felt, predominantly by a midwestern and western group of academic anesthesiologists, that there had to be staying power in the importance to the academic community of research, teaching, and those common interests in the university to justify and support the development of the new Association. The response to the negative pressures of the ASA were not enough reason, in their view, to form a new group. The leaders in these concerns were Cullen, Haugen, and Faulconer. They were satisfied by free and frank discussions of the issues after dinner at the end of the meeting that the AUA was to be an important positive force in fostering the interests and goals of academic anesthesiology.

Each of the founding members was given the task of conducting small, informal group discussions, and the candid answering of questions transpired. These discussions were effective and were a major positive force in the launching of the AUA. It is important to state that Dripps was a major figure in the persuasion of those few leaders who had reservations that needed to be satisfied, despite his initial wariness of even including some of them in the AUA. There is still in my mind a vivid memory of seeing him about to depart from the site of the discussions wearing a hat, a coat and having removed his shoes, possibly as an aid to inspired cerebration, talking earnestly with Cullen and with Haugen about their reasonable and understandable reservations. When Dripps put his shoes on to leave, it seemed that all had been satisfactorily explained and that the group of 37 were now on their way to the very important role of pleasant guidance of the academic community in anesthesiology to a new way of looking at their problems together. They were ready to enhance their personal and professional relationships so important to the development of the intellectual aspects of the specialty.

Therefore, at the Boston meeting, the Association was started under the best of auspices with a high spirit of enthusiasm for common goals that were destined to become important in the development of academic anesthesiology.

Although born in political controversy and enveloped in economic pressures, the important positive elements of commonality in the intellectual and educational aspects of anesthesiology became powerful forces for the development of a strong Association of University Anesthetists. The name would be, in due course, changed to the Association of University Anesthesiologists when the sting of names and the spelling of anesthesia became less important symbolically. Lamont's adherence to conservative naming and the use of the diphthong in the spelling was eventually to disappear.

The quarrel with the ASA rapidly and unemotionally disappeared to the point where AUA members were, in effect, the editors and publishers of the two major journals in anesthesiology and were also the principal providers of the scientific parts of the ASA's annual meeting. AUA members became elected officers in the ASA, and a feeling of mutual tolerance rapidly evolved to mutual respect and then to coordination of activities. The ABA became, in turn, dominated by the academic community and all restriction and threats associated with its previous political behavior disappeared and were no longer negative factors. The AUA, therefore, was rid, in fairly rapid time, of the negative forces that encouraged its development. It was able to pursue the positive purposes of attention to research, to education, and to the commonality of university problems without the need of dealing with serious hostile forces. The AUA quickly became a success in function. The goals of academic anesthesiologists now included election to membership in the AUA.

However, even at the beginning, despite these great successes, there were signs of potential problems and troubles that were to surface in the future. Anesthesiologists, especially academic ones, seem to be excessively introspective, at least as compared to their colleagues in other fields. They seem to react and, perhaps, overreact excessively to negative forces with too much vigor. Their language is, in general, more extreme than that of many others. They don't appreciate sufficiently their own or their colleagues' talents. They underappreciate and underreact to positive strengths. They are constantly trying to find out why they are often uneasy and engage in constant efforts of "reform." Excessive aloofness was once a criticism against the AUA, directed especially against some of its more influential members. As understanding and friendships developed, the AUA began to brood about the excessively social behavior of some of its members. They criticized themselves and their Association of becoming a pleasant inactive status-seeking club where perhaps excessive drinking took place too often. These concerns then were replaced in time by the question of whether democracy, defined as more numbers in the AUA, was healthy for an organization or whether only merit should be the standard for membership. If the latter, how was it to be defined and measured? The subject of age limitation raised its head from the beginning and has continually confronted the membership. How does one decide when a person is no longer as vigorously productive as previously, and in what fields, and by what standards? These are all besetting questions to academic anesthesiologists. They are not really unique to our specialty, but we worry about real and phantom difficulties more than most.

However, the AUA is fortunate in a very important respect. It is charged, generally, by its founders with engaging in common and coordinated efforts in teaching, research, *and all other matters that concern the university community*. Its charter, therefore, gives it free reign to engage in any aspects that the current membership believe important to the work and responsibilities of the academic anesthesiologist without the obstruction of the heavy hand of the past or the reaching out from the grave to dominate current thinking.

The search for renewal of excitement goes on and has from the beginning. Much of it is healthy. However, some of it must be a form of combat with what most generously might be characterized as boredom with peace. The AUA was begun in an environment that included passion. Passion grafted onto intellectual strength will never lose value for the human condition. Each generation must and will decide for itself where the margins are and what issues they need to address. The founders did not have the gift of prophecy, but they recognized the need to address central issues and to permit the felicitous quality of flexibility and responsiveness to constructive change in a future without limitations.

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Failure of Multiple Test Doses and Techniques to Detect Intravascular Migration of an Epidural Catheter

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Recognized intravascular placement or migration of an epidural catheter remains one of the most common complications of epidural anesthesia, occurring in 3%–9% of obstetric patients (1,2). Both a sensitive and specific test dose is lacking, requiring the obstetric anesthesiologist to use multiple test doses and techniques for this purpose. We report a case of a pregnant patient who had a functioning epidural anesthetic for labor in whom a seizure developed after reactivation of the epidural anesthetic for cesarean section. This occurred despite using every commonly used test dose and technique for determining intravascular injection.

Case Report

A 28-yr-old healthy primagravida woman at term was admitted to labor and delivery. After 7 h of labor, the patient's cervical examination disclosed a 3-cm dilation and oxytocin was started. An epidural anesthetic was administered without difficulty through a 17-gauge Tuohy needle placed in the epidural space at L2-3 using a loss of resistance technique. Three milliliters of 0.25% bupivacaine was injected through an open-end single-port epidural catheter. After a negative aspirate for blood, fentanyl, 100 μg, and 0.25% bupivacaine, 6 mL, were injected over 6 min. Subsequently, a continuous epidural infusion of 0.0625% bupivacaine with fentanyl, 2 μg/mL, was initiated at a rate of 10 mL/h. The patient had excellent labor analgesia until 4 h later, at which time she began feeling her contractions. The epidural was reactivated with 0.5% bupivacaine, 5 mL, after negative aspiration; and she again became very comfortable. An intrauterine pressure catheter was then placed, and a 3-min episode of fetal bradycardia and worsening variable decelerations followed. The obstetrician decided to perform a primary cesarean section for fetal distress and macrosomia. The patient was brought into the operating room, moved herself to the operating table, and was placed supine with left uterine displacement. After negative aspiration, a 3-mL test dose of pH-adjusted 2.0% lidocaine with 1:200,000 epinephrine was given through the epidural catheter. No change in heart rate, arterial blood pressure, or sensorium were noted. After 3 min, the patient was given pH-adjusted 2.0% lidocaine with 1:200,000 epinephrine, 5 mL, without change in signs or symptoms. Fentanyl, 100 μg, was given through the epidural catheter with no change in sensorium. Three minutes later another 5 mL of pH-adjusted 2.0% lidocaine with 1:200,000 epinephrine was administered without a change in vital signs. After 3 min an additional 5 mL of pH-adjusted 2.0% lidocaine with 1:200,000 epinephrine was injected through the epidural catheter (total dose 18 mL of pH-adjusted 2.0% lidocaine with epinephrine and 100 μg of fentanyl). Before each dose of lidocaine, no blood could be aspirated from the epidural catheter, and after injection, there were no changes in arterial blood pressure, heart rate, or mental status. Two minutes after the last dose, the patient began shaking and asked, "What's happening to me?" She then had a grand mal seizure. She was given 100% oxygen via a face mask, thiopental, 300 mg, and succinylcholine, 100 mg, IV; and the trachea was rapidly intubated while maintaining cricoid pressure. A fetal bradycardia occurred 1 min after the seizure and continued until cesarean delivery 8 min later. Newborn Apgar scores were 7 and 9 at 1 and 5 min, and the umbilical cord gas values were as follows: umbilical vein: pH 7.17, Pco_2 78 mm Hg, Po_2 13 mm Hg, HCO_3 29 mEq/L, base excess −2.4 mEq/L; umbilical artery: pH 7.15, Pco_2 85 mm Hg, Po_2 6 mm Hg, HCO_3 30 mEq/L, base excess −2.1 mEq/L. After delivery of the baby, general anesthesia was maintained with nitrous oxide and oxygen, IV fentanyl, and a succinylcholine drip. The surgery took 31 min. After extubation of the trachea, the patient immediately complained of pain and had no evidence of any motor or sensory block.

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Postoperatively, only blood-tinged fluid was noted during aspiration and careful removal of the epidural catheter. Both mother and baby had an uneventful postoperative course.

Discussion

Unrecognized placement or migration of an epidural catheter and the subsequent injection of a toxic dose of local anesthetic is a devastating complication of epidural anesthesia. Although it is impossible to know exactly when the epidural catheter migrated into a blood vessel in this case, the epidural catheter was properly located after the initial placement and during the next 4 h of continuous infusion because the patient had good labor analgesia during this time. The need for a "top-up" dose is not uncommon for laboring patients on epidural infusions and does not necessarily mean that the catheter is in a blood vessel. In this case, the patient again became comfortable after the 0.5% bupivacaine, 5 mL, top-up dose, which indicates a functioning epidural catheter. The catheter must have migrated into a blood vessel sometime after the top-up dose and before medication for the cesarean section was given. If some of the lidocaine or fentanyl had been injected into the epidural space, postoperatively the patient should have had only minimal discomfort and exhibited evidence of a sensory or motor block.

Because the patient was on the operating table for a cesarean section when the seizure occurred and had no obvious airway problems, a rapid sequence induction with general anesthesia was chosen to both treat the seizure and for anesthesia for surgery.

All three of the most commonly used techniques to detect an intravascular epidural catheter were used in this case: (a) aspiration (3), (b) fractionation of dose (3), and (c) the use of 15 μg of epinephrine as a test dose (4–7). In addition, two other recently described test doses were used: the administration into the epidural catheter of lidocaine, 100 mg (8), and fentanyl, 100 μg (9).

Aspiration and fractionation have poor sensitivity for identifying intravascular placement, failing to detect 65 of 195 and 12 of 51, respectively, of intravascular epidural catheter placements in one review of 4003 obstetric epidural anesthetics (2). Epinephrine, 15 μg, has been proposed by Moore and Batra (7) as an effective intravascular test dose in nonpregnant patients. Leighton et al. (10), however, has cautioned about the limitations of epinephrine as a marker of intravascular injection in laboring women. Lidocaine, 100 mg, has been proposed by Roetman and Eisenach (8) to have 100% sensitivity and 95% specificity in a study of 20 healthy male volunteers for identification of intravascular placement of an epidural catheter. Fentanyl, 100 μg, has recently been proposed as a highly sensitive test for intravascular placement in laboring women (9). In this case report, all of the above test doses and techniques were used; and yet, we were unable to detect the intravascular migration of an epidural catheter.

Lidocaine plasma levels of 5.29 ± 0.55 μg are associated with generalized twitchings, convulsions, severe breathing difficulties, total disorientation, or loss of consciousness in healthy male volunteers (11). Although lidocaine levels were not obtained, an intravascular epidural catheter was evidenced by the symptoms and the lack of any sensory or motor block at the conclusion of surgery. The threshold for central nervous system symptoms with IV lidocaine has been described by Covino and Vassallo (12) as 6.4 mg/kg or 350 mg in this patient. Our patient received a total of 360 mg of lidocaine over 10 min. In addition, the patient had received 72.5 mg of bupivacaine during the 5 h before being given lidocaine. As local anesthetic toxicity is additive (13), the prior administration of bupivacaine may have contributed to the seizure.

Leighton et al. (14) have shown that 1 mL of air injected into an intravascular epidural catheter can be detected with 100% sensitivity by a precordial Doppler. Perhaps this test would have been useful in our patient. Continuous fetal monitoring during reactivation of the epidural catheter might have demonstrated a decrease in contraction amplitude or change in fetal heart rate as a harbinger of intravascular toxicity.

This case demonstrates the failure of multiple epidural test doses and techniques in a well-monitored patient to detect intravascular migration of an epidural catheter. It should serve to remind us that it is not possible at present to identify intravascular placement or migration of an epidural catheter in all patients.

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The Sellick Maneuver Causing Complete Airway Obstruction

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The Sellick maneuver is designed to protect the airway against aspiration of gastric contents before tracheal intubation and in an emergency to permit safe ventilation via a mask (1). For this maneuver itself to prevent ventilation is highly unusual. We report an adult patient in whom tracheal intubation was defeated by an undiagnosed supraglottic mass, and whose airway was completely obstructed by the application of the Sellick maneuver.

Case Report

A 27-yr-old multigravida patient at term was admitted for elective repeat cesarean section. She was not in labor. She had had two previous cesarean sections: the first, under endotracheal general anesthesia in 1982 and the second under epidural anesthesia in 1986, both without complication or technical difficulty recorded. After the first pregnancy, her weight increased by approximately 20 kg over 12 mo. During the present pregnancy, preeclampsia was suspected because of marked edema, although other criteria of preeclampsia were absent. Preoperative examination revealed an obese patient with marked perioral and other facial edema, but with normal vital signs. Examination of the airway demonstrated greater than two fingers' separation between the mentum and the hyoid. The patient could open her mouth widely enough to permit visualization of a large tongue, swollen fauces, soft palate, and uvula. The epiglottis could not be observed. Although her external nares were wide, large inferior turbinates were clearly visible showing little free air space. Overall, she was judged, by the Mallampati et al. classification, to have a class 2 airway (2).

Ranitidine (50 mg IV), metoclopromide (10 mg IV), and bicitrate (30 mL orally) were administered before anesthesia. An epidural catheter was placed without difficulty at the L3-4 level before transport of the patient to the operating room. However, adequate analgesia was insufficient to permit surgical incision. The decision was then made to induce general anesthesia using a rapid sequence technique. Direct laryngoscopy was attempted with a MacIntosh No. 4 blade while cricoid pressure was applied by the attending anesthesiologist. On laryngoscopy, macroglossia, large pitted tonsils, an edematous, rounded fleshy epiglottic area, and a narrow, bell-shaped epiglottic tip could be exposed; the arytenoids and larynx could not.

Because the hemoglobin desaturated rapidly from 99% to 70% and ventricular ectopy developed, laryngoscopy was discontinued. Ventilation via a mask with 100% oxygen was initiated with cricoid pressure still applied. However, ventilation via the mask was impossible until the cricoid pressure was fully released. No intermediate level of cricoid pressure would permit oxygen flow. Placement of an oral airway did not improve the situation. By that time, oxygen saturation had fallen to less than 40%. Upon complete release of cricoid pressure, ventilation immediately became easy, and oxygen saturation returned to initial values. Repeat laryngoscopy attempted by the attending anesthesiologist was equally unsuccessful. Moreover, in the circumstances, blind nasotracheal intubation was deemed unsafe because of the likelihood of bleeding due to mucosal edema and obviously large inferior turbinates. Although other options for airway management were considered (needle cricothyrotomy with jet ventilation), the decision was made to abort the procedure after consultation with the attending obstetrician. The patient recovered completely from general anesthesia without adverse sequelae. Fetal heart tones were judged to be normal, indicating no adverse effects.

The following day, fiberoptic laryngoscopy revealed a large mass at the base of the tongue, deforming the epiglottis and pushing it with the larynx posteriorly. Unfortunately, photographs of the lesion were not obtained. The patient then underwent an

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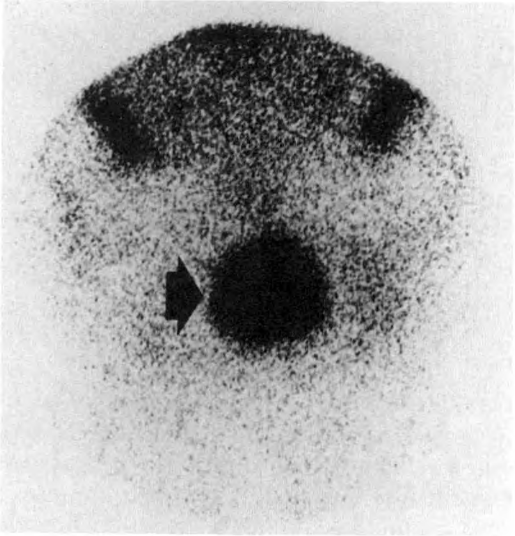

Figure 1. ^{99m}Tc-pertechnetate scintigraphic image, anterior acquisition, lower face and upper neck. Midline circular uptake (*arrow*), diagnostic of lingual thyroid. Activity at 10 o'clock and 2 o'clock represents normal parotid accumulation.

uneventful cesarean section with epidural anesthesia, the catheter being placed in the operating room. An otolaryngologist was present in case emergency tracheostomy became necessary. The newborn was healthy with Apgar scores of eight and nine. There were no further complications.

Because the mass was presumed thyroid tissue, a thyroid scan was performed (Figure 1). Thyroid function studies were consistent with compensated hypothyroidism (thyroid stimulating hormone = 51.8 [normal, <5 μIU/mL], T_3 = 23 [normal, 35%–45%], T_4 = 9.5 [normal, 5–12 μg/dL]), and thyroid replacement therapy was initiated.

Discussion

Ball valve obstruction of the glottic opening by cancer has been reviewed recently (3). Massive facial trauma can cause the same effect, but in both cases the potential for obstruction should be obvious to the anesthesiologist. However, the presence of a mass at the base of the tongue may be less obvious. Airway examination in our patient before induction of anesthesia revealed a large tongue with edematous fauces and uvula. Perhaps the fact that she could open her mouth widely, and the hyoid was positioned greater than two finger breadths below the mandible, gave us a false sense of security. Yet, the presence of a large mass at the base of the tongue did not become apparent until laryngoscopy.

The differential diagnosis of such a mass includes lingual thyroid, benign tumors (e.g., angioma, adenoma, fibroma, and lipoma), and malignant lesions including lymphosarcoma. In an otherwise normal patient, however, the most common mass is lingual thyroid (4). Our patient underwent scintigraphy because thyroid tissue avidly takes up ^{99m}Tc-pertechnetate, thereby absolutely confirming the diagnosis. The size and position of the thyroid image shown in Figure 1, relative to the parotid images nearby, indicates a large ectopic thyroid mass.

Lingual thyroid was first described in 1869 by Hickman (5) in a case dramatically similar to our own. The prevalence ranges from 1:100,000 to 1:300,000 in the general population (6,7) and 1:4000 in patients with known thyroid disease (8). Females account for 75%–89% of all patients harboring lingual thyroids (9,10). Approximately 15% of these patients are hypothyroid at the time of diagnosis (11).

Embryologically, the thyroid bud migrates caudally contacting the aortic sac. With the elongation of the great vessels, the bud assumes its final position below the larynx. The line of descent defines the thyroglossal duct that originates in the foramen cecum at the base of the tongue. Although, ectopic thyroid tissue may appear in any position from the base of the tongue to the mediastinum, lingual thyroid represents totally failed migration. Eighty percent have no other thyroid tissue (7,10). The natural history of lingual thyroid is to hypertrophy in compensation for reduced function. The increased metabolic demands of pregnancy cause further hypertrophy.

In fact, our patient had a hypertrophied lingual thyroid with subclinical hypothyroidism at the time of examination. The mass prevented access to the larynx during laryngoscopy and acted as a ball-valve, obstructing the airway when cricoid pressure was applied. The Sellick maneuver was performed by a senior faculty member experienced in both its application and its teaching. There was no reason to suppose that cricoid pressure was improperly applied. That being the case, we hypothesize that in the circumstances, backward movement of the cricoid cartilage was translated into a pivoting forward of the glottic opening against the tumor and grossly distorted epiglottis, the hyoid bone becoming the fulcrum. We would suggest that edema and the tumor had almost consumed all of the volume embraced by the hyoid. With the stylohyoid ligaments nondistensible, and rearwards motion restricted by edema and tissue distortion, further movement at the distal end of the glottic funnel would pull the anterior part of the hyoid body down, thereby rotating the glottic opening into the ball created by the tumor, thus causing the epiglottis to occlude the entrance. Yet, during spontaneous respiration, the patient had neither symptoms nor signs of frank airway obstruction, and upon release of cricoid pressure ventilation was easy.

Review of the medical records from the prior deliveries over the previous 7 yr disclosed no reported airway problems associated with anesthesia. By our patient's third pregnancy, however, thyroid hypertrophy sufficient to impede tracheal intubation had occurred. Therefore we infer that her earlier pregnancies had not yet caused sufficient hypertrophy of the lingual thyroid to compromise laryngoscopy. Clinically, she had not presented with signs of obvious hypothyroidism; however, in retrospect her weight gain and edema had spuriously been attributed to pregnancy itself.

Faced with an airway obstructed by the Sellick maneuver in an obese, pregnant patient, whose hemoglobin was rapidly desaturating, we had no choice but to release the cricoid pressure to ventilate via a mask. We judged that the risk of asphyxia in both mother and fetus outweighed that of aspiration. Had the procedure been an emergency, our options would have been limited either to proceed without airway protection or to perform immediate cricothyrotomy. In our patient, other approaches to the airway were blocked by nasal obstruction, and the rapid rate of hemoglobin desaturation discouraged more-time-consuming procedures. Aborting when we did seemed the most appropriate choice.

The Sellick maneuver is performed to protect the airway during rapid sequence induction of anesthesia. Maintaining the maneuver while ventilating via a mask is accepted practice when intubation has failed. To be unable to ventilate under such circumstances is unnerving and points out the absolute necessity of a systematic evaluation of the airway in all patients undergoing anesthesia, whether general or regional—more so in the parturient. For the Sellick maneuver to cause complete airway obstruction, a supraglottic ball-valve mass should immediately be considered. Lingual thyroid is the most reasonable diagnosis in an otherwise normal patient.

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Removal of a Large Intrathoracic Tumor in a Child: Neurogenic Motor-Evoked Potential Monitoring of Spinal Cord Integrity and Anesthetic Management

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Neurogenic tumors are the most common mediastinal neoplasms (1). These tumors may occur at any age, but they carry a higher risk of malignancy in children. Ganglioneuromas are the most common mediastinal neurogenic tumors. They are benign and generally asymptomatic (2). However, approximately 10% of patients with neurogenic tumors experience growth of the paravertebral mass through the intervertebral foramina with a significant portion of the tumor located intraspinally (3). Removal of these neoplasms risks potential spinal cord injury owing to the presence of the tumor adjacent to and within the spinal canal. The combined neurosurgical and thoracic posterior approach presents a unique challenge to the anesthesiologist. We describe neurogenic motor-evoked potential monitoring (NMEP) of spinal cord integrity in a small child. In addition, we report a unique method of providing one-lung ventilation in the pediatric patient.

Case Report

A 4-yr-old, 16.8-kg girl was scheduled for removal of a large intrathoracic tumor. She was admitted with a 3-mo history of recurrent right upper lobe pneumonias. A large intrathoracic mass was noted on a chest roentgenogram, and a subsequent magnetic resonance imaging of the thorax showed a 5 × 7-cm posterior mediastinal mass spanning thoracic vertebrae T3-7 with spinal canal involvement (Figure 1). The remainder of the history and physical examination was noncontributory. Laboratory values were within normal limits, and no evidence of neurologic impairment was evident.

In the operating room, standard monitoring was used. Anesthesia was induced with thiopental, 80 mg, and fentanyl, 5 μg/kg IV. After adequate muscle relaxation was obtained with succinylcholine 1 mg/kg, the trachea was intubated with a 5-mm cuffed endotracheal tube, and ventilation was controlled. Additional 18-gauge intravenous cannulas were inserted into the right hand and the right foot. A 22-gauge left radial arterial cannula and a right internal jugular vein triple-lumen catheter were inserted. Anesthesia was maintained with a continuous IV fentanyl infusion of 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and 0.5–1.0 MAC isoflurane. Before induction, a 5F Fogarty catheter was inserted through a ventilating bronchoscope adapter into the endotracheal tube and was advanced until it was flush with the tip of the endotracheal tube. This position was marked on the catheter with tape. After induction, a 3.7-mm flexible pediatric bronchoscope was passed into the endotracheal tube through the bronchoscope ventilating adapter, and the tube was then positioned in the proximal right mainstem bronchus. The bronchoscope was removed, and the Fogarty catheter was inserted through the bronchoscope adapter and was advanced until the tape was flush with the bronchoscope adaptor, positioning the catheter in the proximal right mainstem bronchus. The endotracheal tube was then pulled back into the trachea leaving the Fogarty catheter in the right mainstem bronchus. The right lobe of the lung could then be isolated by inflating the cuff of the catheter with 0.8 mL of saline.

Integrity of the anterior and posterior columns was monitored with sciatic NMEPs and posterior tibial somatosensory evoked potentials (SSEPs). After induction of anesthesia, a standard two-channel SSEP montage was used (CZ′-FPz, C_2). For NMEPs, 12-mm stimulating electrodes were placed percutaneously into the interspinous ligaments of C4-5 (anode) and C6-7 (cathode). With the aid of a peripheral nerve

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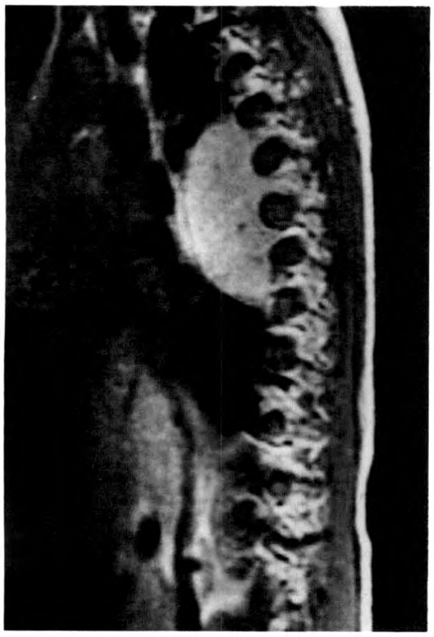

Figure 1. Magnetic resonance image demonstrating encroachment of the tumor on the spinal canal at thoracic vertebral levels T3-7.

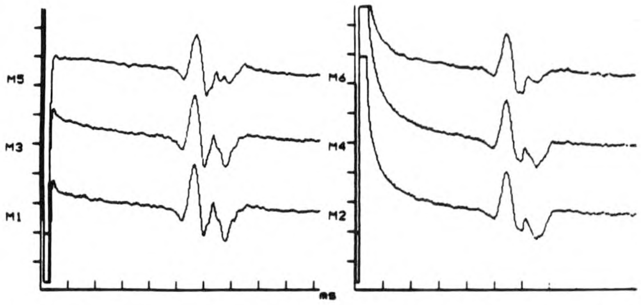

Figure 2. Example of intraoperative neurogenic motor-evoked potential monitoring waveforms. Right-side neurogenic motor-evoked potential monitorings are represented by M1, control; M3, intraoperative with 1.0 MAC isoflurane; and M5, after skin closure. Left-side neurogenic motor-evoked potential monitorings are represented by M2, control; M4, intraoperative with 1.0 MAC isoflurane; and M6, after skin closure. Scale: 2.5 ms/division, 4.88 μV/division.

stimulator, bipolar 20-gauge insulated recording electrodes were positioned over the sciatic nerves bilaterally. A 12-mm ground electrode was inserted percutaneously over the left shoulder. These electrodes were attached to a Nicolet Compac Four (Nicolet Instruments, Madison, Wis.) clinical averager. After placement of all electrodes, neuromuscular blockade was established and maintained with pancuronium bromide. The SSEPs were generated by standard protocol. However, because of electrical interference, cortical SSEPs were of poor quality. The NMEPs were generated with bipolar square-wave pulses at a constant current of 25 mA delivered at a rate of 4.8 pulses/s with a duration of 200 μs. One hundred sweeps were acquired through a band pass of 10–1500 Hz and averaged. Impedance of recording electrodes was maintained at less than 3000 Hz. The resulting signals were recorded on a floppy disk as well as viewed on the oscilloscope. After acceptable NMEPs were generated, isoflurane 1.0 MAC was administered. No changes of the NMEP amplitude or latencies were observed (Figure 2). A right thoracotomy was performed, and a tissue diagnosis of ganglioneuroma was made by frozen section. The incision was extended and the tumor was excised after laminectomies of vertebrae T3-5 were performed. The tumor encased the spinal cord but did not enter the dura. The neurogenic motor-evoked potentials were of high quality and unaffected by changes of anesthetic level or electrocautery. No significant changes in amplitude or latency of the NMEPs occurred during excision of the tumor. One-lung ventilation was easily accomplished by inflation of the Fogarty catheter. An epidural catheter was placed directly by the surgeon, and 1.6 mg of preservative-free morphine was injected. After completion of the procedure, the child was awakened and the trachea was extubated. Motor function was noted to be intact in all four extremities, and the patient was transported to the intensive care unit. Recovery was uneventful, and the patient was discharged on the sixth postoperative day.

Discussion

Loss of spinal cord function is a devastating complication of surgical procedures on the spinal column and aorta. Monitoring of cord function previously required an intraoperative Stagnara wake-up test (4) or methods that monitor the electrical continuity of spinal cord function continuously over the course of a procedure. Although effective, a wake-up test only documents the integrity of function at a fixed point in time. Methods that monitor electrical continuity of spinal cord function allow for continuous monitoring of cord function over the course of a procedure. Somatosensory evoked potential monitoring records electrical continuity of dorsal column (sensory) function but may not detect injury to ventral (motor) pathways (5,6). This is not surprising, considering that the dorsal columns are supplied primarily by the paired posterior spinal arteries, whereas anterior motor columns are perfused by a single anterior spinal artery (7). The presence of a single vessel of variable origin makes the lateral motor columns most susceptible to ischemia. The distant recording site (scalp electrodes) and multisynaptic pathway of SSEP monitoring contrasted with the monosynaptic pathway, and direct nerve recording of the NMEP signal may account for the increased sensitivity of SSEP monitoring to electrical interference observed in our patient.

Monitoring of motor function by stimulation of the brain or spinal cord is now possible. Stimulation can be performed transcranially by electrical or magnetic means. Spinal stimulation may be accomplished through percutaneous or epidural electrodes or through direct application of current to the cord.

Transcranial magnetic stimulation is nonnoxious and may be performed in the awake patient (8). This technique has been applied clinically to successfully monitor pathologic conditions in awake patients and during scoliosis surgery (8,9). Microelectrode recordings indicate that transcranial electric stimulation may actually produce signals generated by extrapyramidal tract fibers that were activated by vertex to hard palate stimulation of the brainstem, rather than the intended stimulation of pyramidal tract fibers (10,11). In addition, transcranial magnetic and electrical stimulation of motor-evoked potentials are very sensitive to the effects of anesthetics (9,12–14). If electromyographic means of signal recording are used, complete neuromuscular blockade must also be avoided. This combination of light anesthesia and absence of paralysis may be fraught with hazard in patients undergoing delicate surgical procedures.

Spinal neurogenic motor-evoked potentials are relatively simple to perform, and they provide valuable information regarding spinal cord motor function. Stimulating electrodes are placed percutaneously above the site of operation at the base of the adjacent spinous processes. Recording electrodes are usually positioned over the sciatic nerves. Recording of NMEP signals within the spinal cord below the level of potential injury is not recommended because antidromic conduction through sensory pathways may conceal motor injury (15). However, recording NMEP signals from peripheral sites, such as the sciatic nerve, does not involve antidromic sensory conduction. Selective spinal cord lesioning in several animal models has demonstrated specificity of the NMEP for primarily pyramidal motor tracts (15–18). The ability of spinal NMEP monitoring to detect and accurately predict motor outcome in humans has also been documented (15,16). Though no prospective evaluations exist, a reduction in NMEP amplitude of more than 50% is considered to be a significant change predictive of outcome and warrants immediate action (reduction of distraction or increased perfusion pressure) (12,19). Latency is insensitive to the effects of mechanical distraction or manipulation of the spinal cord.

An NMEP differs from a myogenic motor-evoked potential in that the recorded response is neurogenic in origin. Thus, muscle relaxants may be administered without compromise in signal quality. The only description of volatile anesthetic effects on NMEP monitoring that reported no significant changes in amplitude or latency used 1.0 MAC halothane (20). However, the signals were recorded within the epidural space rather than at a peripheral site. Peripheral recording provides additional important information because a higher level of functional organization than simple axonal conduction within the spinal cord is required (18). In addition, recording at both sciatic nerves permits detection of unilateral cord injury. The addition of 1.0 MAC isoflurane to the nitrous oxide/narcotic technique used in this patient did not compromise the ability to monitor the peripheral NMEP signal.

The method of unilateral lung ventilation used for this child offers several advantages over techniques reported previously. Deliberate intubation of a mainstem bronchus with a single-lumen endotracheal tube may be problematic. Right mainstem intubation frequently obstructs the right upper lobe bronchus, producing unacceptable levels of arterial hypoxemia. Left mainstem intubation can be extremely difficult but may be facilitated by head manipulation or tube position or by manual alteration of the endotracheal tube to produce a right bevel (21,22). However, when one-lung ventilation is not required, pulling the endotracheal tube back into the trachea may result in an inability to intubate selectively the left mainstem bronchus again.

Previous reports of selective bronchial blockade in children have required two episodes of laryngoscopy or rigid bronchoscopy (23–25). The method used in our patient required a single episode of laryngoscopy with a standard endotracheal tube. By measuring the distance from the bronchoscope adapter to the tip of the endotracheal tube and by marking the catheter, we were able to precisely place the Fogarty catheter. After the endotracheal tube was positioned on the right side above the right upper lobe bronchus, the catheter was inserted to the mark and the endotracheal tube was withdrawn into the trachea. When one-lung ventilation was not required, simple deflation of the catheter permitted ventilation of both lungs without losing the ability to immediately resume lung isolation if necessary.

In summary, we have reported the anesthetic management of a child during removal of a large intrathoracic tumor with spinal cord involvement. A simple and effective means of selective bronchial blockade was used. Spinal cord integrity was continuously monitored by spinal NMEP recorded at the sciatic nerves. Isoflurane had no significant effect on amplitude or latency of the NMEP signal.

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Anesthetic Management of a Child With Noonan's Syndrome and Idiopathic Hypertrophic Subaortic Stenosis

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Noonan's syndrome is a relatively rare hereditary disorder characterized by abnormalities of the facial, cardiovascular, and skeletal systems (1,2). There has been only one case report describing a patient with Noonan's syndrome in which the patient underwent a cesarean section under regional anesthesia (3). In this report we describe the preoperative evaluation and anesthetic management of a child with Noonan's syndrome complicated by idiopathic hypertrophic subaortic stenosis (IHSS), a lesion not typically associated with this syndrome.

Case Report

A 7-yr-old girl was admitted for elective cholecystectomy because of repeated episodes of cholecystitis secondary to cholelithiasis. The diagnosis of Noonan's syndrome was made when she was 18 mo of age. At that time she was admitted with facial abnormalities that included hypertelorism, bilateral epicanthal folds, antimongolian palpebral slant, ptosis, micrognathia, flattening of the midface, low-set ears, and high palatal arch. Chromosomal studies showed her to be genotype 46XX. She exhibited moderate developmental delay, pronounced webbing of the neck, widely spaced nipples, mild lordosis, lower leg edema, short stature, and IHSS. Two years before this admission for surgery, she had complained of fatigue. An echocardiogram performed at that time demonstrated IHSS with a small ventricular septal defect. She had been clinically controlled with 12.5 mg/day of atenolol given orally. The patient had undergone no previous anesthetic. The family history was unremarkable for anesthetic complications or other congenital abnormalities.

Physical examination revealed an alert, cooperative girl who weighed 22 kg (45th percentile for age), and whose height was 93 cm (below third percentile for age). Arterial blood pressure was 100/60 mm Hg, heart rate was 86 beats/min, and respiratory rate was 24 breaths/min. Echocardiogram, performed with sedation and as a nonstressed study, revealed a hypertrophied septum (1.8 cm thick) with concentric hypertrophy of a small hyperkinetic left ventricle. A small high ventricular septal defect and mild left atrial enlargement were noted. There was also muscular subaortic stenosis with a 15 mm Hg subaortic gradient and mild mitral regurgitation. The electrocardiogram was suggestive of left atrial enlargement and left ventricular hypertrophy.

Preoperative analysis of arterial blood gases showed pHa = 7.39, $Paco_2$ = 41 mm Hg, and Pao_2 = 64 mm Hg breathing room air. Evaluation of her airway demonstrated a high palatal arch, moderate degree of micrognathia, dental malocclusion, and a webbed neck. Radiologic studies showed a mild degree of kyphoscoliosis (15°) and lordosis but a normal cervical spine. Hemoglobin was 12.4 g/dL, and serum electrolytes, creatinine, glucose, aspartate transaminase (serum glutamic oxaloacetic transaminase), alanine transaminase (serum glutamic pyruvic transaminase), and alkaline phosphatase were within normal limits.

A fiberoptic laryngoscope as well as a variety of laryngoscope blades were prepared. The patient was orally premedicated with atenolol (12.5 mg) and diazepam (5 mg) 2 h before induction of anesthesia. Before establishing intravenous access, 4 mg of midazolam was administered intranasally. The child readily accepted a 22-gauge intravenous catheter in her left arm after 10 min.

After application of electrocardiograph leads, pulse oximeter (oxygen saturation [Spo_2] = 95%), and noninvasive blood pressure monitors, anesthesia was induced with halothane, nitrous oxide, and oxygen via a face mask. Controlled ventilation was begun, and a right radial arterial catheter was then inserted for continuous monitoring of blood pressure and arterial blood gas tensions if needed. A mild tachycardia of 110 beats/min was controlled with three bolus doses of

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200 μg/kg of esmolol followed by a continuous infusion of esmolol before laryngoscopy. The heart rate returned to preoperative levels of 80–90 beats/min. Paralysis was provided by vecuronium (0.1 mg IV). Three attempts to directly visualize the glottis using a laryngoscope blade were unsuccessful. Endotracheal intubation was finally accomplished by passage of a 3.3-mm Rüsch introducer-stylet into the trachea as a guide followed by the insertion of a 5.0-mm internal diameter, uncuffed endotracheal tube inserted over the introducer. During the attempts at endotracheal intubation, blood pressure, Spo$_2$, and heart rate remained at preinduction levels. Anesthesia was maintained with a mixture of 0.5%–1.0% halothane, oxygen, and air and a continuous infusion of 0.4–0.8 $\mu g \cdot kg^{-1} \cdot h^{-1}$ of sufentanil, 100–300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of esmolol, and 0.05–0.10 $mg \cdot kg^{-1} \cdot h^{-1}$ of vecuronium. Antibiotic prophylaxis was with ampicillin and gentamicin administered intravenously. Ventilation was controlled to achieve an end-tidal CO$_2$ of 35–40 mm Hg, and the Spo$_2$ was maintained between 90% and 100%. Intravenous fluids were initially 20 mL/kg of lactated Ringer's solution followed by aggressive replacement of losses during the intraoperative course. A total of 750 mL of fluid was administered intravenously during the 180-min operation. The estimated blood loss was 30 mL. Reversal of residual paralysis was accomplished with the intravenous administration of 0.2 mg of glycopyrrolate and 1.5 mg of neostigmine. The trachea was successfully extubated during deep general anesthesia. During the immediate postoperative period, the heart rate and arterial blood pressure were maintained within normal limits using a continuous infusion of esmolol. Subsequently, β-adrenergic blockade was maintained by intravenous propranolol followed by oral atenolol. The patient was discharged 3 days after an uneventful recovery.

Discussion

Noonan's syndrome is an increasingly recognized but relatively rare clinical entity that presents with various congenital anomalies. The syndrome has been recognized in phenotypic males who have certain anomalies that also occur in females with Turner's syndrome. Both males and females have normal karyotypes (1,2).

The clinical picture of Noonan's syndrome consists of short stature, webbing of the neck, flattening of the mid-face, hypertelorism, ptosis, epicanthal folds, antimongolian palpebral slant, micrognathia, ear abnormalities, and a "shield-shaped" sternal deformity that gives the illusion of widely separated nipples. In addition, most patients have pectus carinatum or excavatum, cubitus valgus, and frequently, congenital heart disease. The most common congenital lesion is pulmonic stenosis either alone or in combination with a septal defect, usually atrial (1). The association of Noonan's syndrome with IHSS has been previously described (4). Mental retardation, usually mild, is a frequent feature of the syndrome. Renal and skeletal anomalies have also been described. The inheritance may be familial, autosomal dominant, or sporadic, but no chromosome abnormality has yet been found.

The anesthetic considerations and potential problems of the patient with Noonan's syndrome include the possibility of a difficult airway, impairment of cardiopulmonary function, and issues associated with mental retardation and short stature. The potential for airway difficulties in Noonan's syndrome, as encountered in our patient, is based on the redundant thick webbed neck, micrognathia, and high arched palate, as well as other described facial abnormalities (3). Regional anesthesia was excluded in our patient because it was believed that the associated vasodilation might increase the subaortic gradient and further compromise the patient's cardiac output. Furthermore, the child's moderate mental retardation and potential combativeness, coupled with probable technical difficulties associated with the short stature, kyphoscoliosis, and lordosis, made regional anesthesia impractical and potentially dangerous. An awake oral or nasal intubation might have been technically impractical in a struggling child as well as probably difficult due to the described facial abnormalities. Furthermore, the detrimental effects of tachycardia might again compromise cardiac output.

The decision to use a slow inhalation induction followed by controlled ventilation was made after discussion with the parents. A fiberoptic intubation set was available in the event of a failed intubation by direct laryngoscopy. Endotracheal intubation was successfully accomplished using a conventional laryngoscope and introducer.

A cervical spine radiograph is advisable in patients with significant short stature before attempting manipulation of the neck. This is to exclude atlantoaxial instability; otherwise, cervical cord compression may result. Although we are unaware of reports of cervical instability associated with Noonan's syndrome, odontoid dysplasia with atlantoaxial instability occurs frequently in syndromes affecting the axial skeleton (5). If the odontoid process is hypoplastic, the atlas (C1) may dislocate anteriorly and may cause spinal cord compression (3,5).

Congenital heart disease is a common component of Noonan's syndrome. Pulmonic valve stenosis was encountered in all patients in one series (6), and in 30%–50% of patients in another study (7). Coarctation of the aorta and aortic stenosis were present in 25%–40% of patients with Noonan's syndrome in the same reports (6,7). Eccentric hypertrophy, affecting the superior portion of the anterior wall, the septum, or the diaphragmatic portion of the left ventricle, and progressive obstructive cardiomyopathy have been reported previously in association with Noonan's syndrome (5,7). The eccentric hypertrophy frequently is nonobstructive and asymptomatic.

The patient we describe is one of the rare cases in whom the hypertrophy became obstructive and symptomatic (5). A hemodynamically insignificant ventricular septal defect (diagnosed by echocardiogram despite absence of characteristic murmur) was an additional incidental finding in this patient. The degree of dynamic obstruction in IHSS varies with the rate of ejection of blood and the volume of the left ventricle. Obstruction is increased by tachycardia, increased contractility, arterial vasodilation, and decreased preload (8–11). The anesthetic goals therefore include maintenance of appropriate intravascular volume while avoiding direct or reflex increases in contractility or heart rate.

Children and/or mentally retarded patients present the problems of intravenous access and smooth induction to a deep level of general anesthesia, both desirable conditions for induction in these patients. Intravenous access and maintenance of adequate preload were accomplished after premedication. Fluid (20 mL/kg) was given just before induction to increase preload. Laryngoscopy was attempted only after achieving deep levels of inhalational anesthesia and the administration of esmolol. This was to prevent catecholamine release or increases in sympathetic nervous system activity and tachycardia, which might otherwise have increased the subaortic pressure gradient (8).

The respiratory system is often compromised in patients with Noonan's syndrome because of the "shield-shaped" chest, pectus deformity, kyphoscoliosis, and short stature (1,2). Preoperative evaluation should include chest roentgenogram, arterial blood gas determinations, and/or pulmonary function studies in these patients. This assessment may be helpful in predicting the need for postoperative ventilation, intraoperative monitoring, and management. In this case it was decided to insert an arterial catheter for continuous monitoring of blood pressure as well as arterial blood gases if necessary. The low preoperative $\mathrm{Pa}_{\mathrm{O}_2}$ value obtained breathing room air was considered to be most likely due to right-to-left shunting via the ventricular septal defect, which increases when the child cries in response to arterial puncture. Because the degree of kyphoscoliosis was mild, an increased (A-a) CO_2 gradient was thought to be unlikely. Ventilation was adjusted according to the monitored end-tidal CO_2.

The patient with Noonan's syndrome may also have a variety of orthopedic abnormalities (1,2) that should be considered in planning the anesthetic. In addition to kyphoscoliosis and short stature, patients may exhibit cubitum valgum, clinodactyly, and vertebral anomalies that may affect positioning, protection of pressure points with padding, intravenous access, and choice of anesthetic technique (regional versus general anesthesia).

In summary, patients with Noonan's syndrome may have a variety of anomalies, some of which present challenging anesthetic dilemmas. Preoperative evaluation should include a thorough evaluation of the airway and cardiovascular system. The anesthetic plan should consider the above anomalies and be designed to prevent further complications. Inhalation induction of anesthesia allows airway control and maintenance of a low left ventricular outflow pressure gradient. Halothane and β-adrenergic blockers are useful and well tolerated in most patients with IHSS. Adequate administration of intravenous fluid is advisable to prevent increases in the subaortic gradient.

We thank Jonathan V. Roth, MD, and Peter Mamunes, MD, for their review of this manuscript.

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Letters to the Editor

Transillumination to Facilitate Venipuncture in Children

To the Editor:

Venipuncture in neonates and infants is often a rate-limiting step in the performance of a smooth anesthetic. Children who are obese, darkly pigmented, or chronically ill may pose a challenge to successful venipuncture even after the administration of a vasodilating inhaled anesthetic. Originally used as an aid to the diagnosis of hydrocephalus, Kuhns et al. (1) visualized vascular anatomy by transillumination through the subcutaneous tissue. As most transilluminating devices require electrical outlets, the patient is exposed to possible thermal injury from prolonged contact. Furthermore, they are bulky to use. Thus, they have not found widespread application for routine venipuncture.

By using two closely positioned fiberoptic lights, a venous transilluminator (Landry Vein Light, Applied Biotech Products, Lafayette, La.) effectively illuminates nonvisible veins under the skin without the danger of thermal injury (Figure 1). The venous transilluminator focuses two intense light beams at an adjustable distance into and beneath the skin to localize the dark venous structures. These absorb some of the intense light and are highlighted from the soft tissues. After dimming ambient light, the venous transilluminator is turned on and the fiberoptic arms scan over the skin surface to visualize underlying structures. The most reliable areas are the forearm, the dorsum of the hand, and the volar surface of the wrist, all of which readily display their superficial venous anatomy. After tourniquet application and localization of a suitable vein, the light source arms are finely adjusted to maximize enhancement of the venous outline and the instrument is fixed in position with a Velcro strap. Venipuncture with a 22-gauge catheter for infants and a 24-gauge for newborns and prematures is then accomplished in the customary fashion. In premature infants, the relative absence of subcutaneous fat and the diaphanous nature of the skin permits easy access in all parts of the extremities.

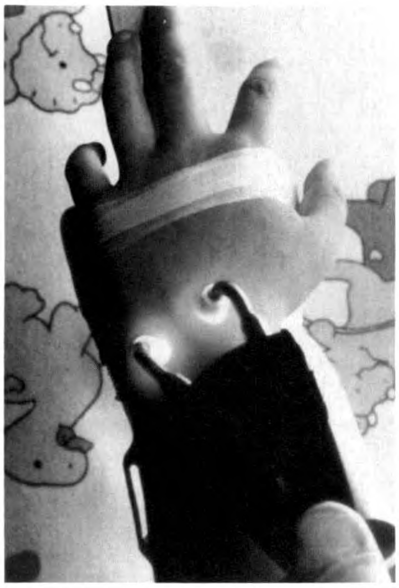

Figure 1. The transilluminator highlighting a vein on an infant's hand.

After facility is gained, venipuncture is usually successful on the first attempt. The technique cannot be extended to assist in the percutaneous placement of an arterial catheter. Light absorption from the pulsating arteries does not readily occur as they are deeper and lighter than the veins (2).

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False-Positives With the End-Tidal Carbon Dioxide Detector

To the Editor:

We read with interest the article by Ping et al. (1), which suggests that capnography lacks some of the attributes of the ideal monitor for detecting esophageal intubation. The authors clearly demonstrate that CO_2 waveforms are observed after intragastric administration of a carbonated beverage. We wish to point out that the recently introduced Easicap (Nellcor Inc., Hayward, Calif.) disposable end-tidal CO_2 detector (2) may also exhibit this potential hazard. Here, a color change indicating correct tracheal tube placement can occur on exposure to low concentrations of CO_2, even though the endotracheal tube has actually been placed in the esophagus. These false-positive situations can potentially also occur with the CO_2 detector after ingestion of carbonated beverages such as Diet Coke, Classic Coke,

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Pepsi, 7 Up, carbonated mineral water, and the antacids Maalox and sodium bicarbonate.

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In Response:

We agree completely with the comments of Drs. O'Flaherty and Adams. Disposable end-tidal CO_2 detectors are semiquantitative capnometers and may not identify an esophageal intubation as readily as capnography. An abnormal CO_2 waveform provided by a capnograph may be the only early clue to identifying an esophageal intubation. It must, nevertheless, be remembered that a normal CO_2 waveform during the first few ventilations is not synonymous with a properly placed endotracheal tube.

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Epidural Morphine in a Small Community Hospital: A False Sense of Security

To the Editor:

I read with interest the paper by Cross and Hunt (1) describing the feasibility of using epidural morphine for postoperative analgesia in a small community hospital. In similar circumstances, that is to say a 200-bed general hospital with the duty anesthetist within 10 min at night, we successfully and safely use intermittent boluses of 4-mg preservative-free diamorphine in 10-mL saline via an indwelling lumbar epidural catheter for postoperative analgesia. We have experienced no major complications, and the incidence of minor complications, as substantiated by the literature (2–6), is entirely acceptable. Indeed, the incidence of nausea and consumption of antiemetics is less in these patients.

However, I believe that there are several serious flaws in the practice described by the authors. A review of the use of epidural morphine (7–9) shows ventilatory depression to be clearly associated with patients older than 70 yr, thoracic epidurals, preexisting reduced ventilatory capacity, and concomitant administration of systemic opiates. Despite this body of experience, 15 of the 52 patients were older than 70 yr and peroperative concomitant opiates were used freely. The authors ask, but do not answer the question "would our incidence of complications be unacceptably high compared with the more traditional use of parentral opiates?" I would suggest that 2 of 25 patients requiring the treatment of respiratory depression with naloxone immediately postoperatively is considerably higher than would be expected in similar patients managed conventionally.

The authors correctly comment that the potential early respiratory depression in all postoperative patients dictates a high degree of monitoring in the anesthetic room. In this environment, they were happy to administer supplementary parentral morphine. However, epidural morphine exhibits biphasic respiratory depression (10) and further IV boluses of morphine seem to be administered outside the recovery room. In a few patients additional epidural opiates (hydromorphone, fentanyl, and sufentanyl) were used, producing what must be a quite unpredictable cocktail. To accept a lesser degree of monitoring in these circumstances is illogical.

We are successful in the use of an epidural opiate technique because we use an opiate with more favorable physical properties and pharmacokinetic profile (11–14), the minimum monitoring of each patient is by nurse observation and pulse oximetry, we administer supplementary oxygen continuously, and we avoid the concomitant use of parentral opiates. Nonsteroidal antiinflammatory agents, intramuscularly or rectally administered, are useful adjuncts.

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In Response:

We appreciate the opportunity to respond to Dr. Spittal's comments regarding our paper (1). To start, we would like to clarify a few basic facts that we apparently did not make clear in our paper, and then we would like to discuss some of the more philosophical points raised by Dr. Spittal.

First, we used no thoracic epidurals in our acute pain service (APS). Second, as we stated, our dose of epidural morphine was tailored to the age, overall condition of the patient, and degree of pain relief obtained. Third, we had a total of three patients out of the 52 that we reported in detail in whom clinically significant respiratory distress developed (two in the postanesthetic recovery room and one delayed). This does not translate into 2 of 25, even counting the acute cases. However, our total APS population at the time was more than 150. There are now well over 300 patients included in the APS with no recurrences of delayed respiratory depression, making the incidence about 0.3% to date. Fourth, the comparison of delayed respiratory depression with early respiratory depression in the postanesthetic recovery room is inappropriate. The need for low-dose naloxone reversal of clinical respiratory depression after opioid-based general anesthesia is certainly not a rare occurrence (2,3) even in the absence of epidural opioids. Because of the very nature of postanesthetic recovery areas, we believe the use of epidural opioids need not exclude per se the use of intraoperative parenteral opioids.

Dr. Spittal states that diamorphine has a much better pharmacokinetic profile for clinical safety than morphine. Although a discussion of less favorable parts of that profile (such as duration of action) might be of interest, the overriding consideration is that diamorphine (heroin) is an illegal drug in the United States and is unavailable for clinical practice. Therefore, any comparison of benefits between morphine and diamorphine would be merely an academic exercise.

We are certainly aware of the diphasic nature of the respiratory depression produced by epidural morphine. This does not mean that they are all clinically significant. Subjects in the paper cited by Dr. Spittal (4) were nonsurgical patients with chronic low back pain and were injected with a dose of morphine larger than is customarily used in our APS. It is understandable to us that clinically significant respiratory depression occurred in 1 of 7 patients in that study.

In clinical practice, the primary goal of pain management is pain relief. We see little justification for demanding that the patient's pain be relieved by a preselected dose based on the opioid type and route of administration. Therefore, we occasionally elected to administer supplemental opioids as needed to provide adequate pain relief. These were either (a) fat-soluble opioids with a more rapid onset but shorter duration of action administered epidurally with morphine to hasten the onset of pain relief, or (b) parenteral morphine administered to give temporary pain relief when the epidural morphine began to wear off before the catheter could be reinjected. Such a management regimen has not resulted in any cases of clinical respiratory depression in the APS to date (our one patient with delayed respiratory depression received no supplemental narcotics).

Although Dr. Spittal refers to a "lesser degree of monitoring," the fact is that there is still no "standard of monitoring" established for patients receiving epidural opiates. We can only refer Dr. Spittal back to references in our original paper that show parenteral morphine to cause a significant incidence and severity of hypoxemia in closely monitored postoperative patients, and an added reference quoted by Dr. Spittal (5) that associates parenteral morphine with an "unstable pattern of arterial oxygen saturation." Therefore, before patients receiving epidural opioids are subjected to a "higher standard of monitoring," one should show that (a) the risk of clinical respiratory depression associated with epidural opioids is significantly higher than that of parenteral opioids, which could warrant the added expense and inconvenience of added monitoring, and (b) that the added monitoring will make a difference. We are not aware of any studies that prove either point.

Moreover, in our experience, problems associated with the use of pulse oximeters and apnea monitors made their use both ineffective and potentially dangerous when used to monitor postoperative patients receiving epidural opioids. Postoperative patients move around, causing a high incidence of false alarms. The incidence is even higher if one sets the oximetry alarm at an oxygen saturation one considers "safe" (90 or above). It is human nature eventually to ignore alarms under such circumstances. Worse yet, the alarm at the patient's bedside is often inaudible at the nurses' station. Not only are studies lacking that show that added monitors make a difference in detecting delayed clinical respiratory depression in patients receiving epidural opioids, we see even less justification for the costs of a "higher standard of monitoring" for these patients when the "higher" standard may be unreliable and, by its presence, lead to a false sense of security. As vigilant nursing observation is needed regardless of the route of opioid administration, we elected to monitor patients only by that method. The adequacy of the policy has been confirmed by our clinical experience and that of others as referenced in our original paper. The fact that Dr. Spittal states that he has not experienced any major complications makes us wonder whether routine pulse oximetry has proven itself to be essential in his practice as well. On a similar note, Dr. Spittal's standard of providing supplementary oxygen to all his patients receiving epidural opioids is commendable. However, are other patients who receive only parenteral opioids not likewise at risk for hypoxemia and deserving of an equal standard of care?

Respiratory depression is an inevitable complication of postoperative opioid therapy and clinically significant respiratory depression will develop in an occasional patient regardless of the route of administration. Therefore, the effectiveness and safety of any APS should be evaluated by asking (a) whether adequate pain relief is obtained in postoperative patients at an acceptable incidence of clinically significant respiratory depression compared to conventional opioid administration, and (b) whether the APS policies include effective means of detection and allow appropriate treatment of complications without unnecessary discomfort, cost, or inconvenience to the patient. We believe that in our APS, both questions have been answered affirmatively.

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Epidural Anesthesia in Patients With Klippel-Trenaunay Syndrome

To the Editor:

We read with interest the case report by Eastwood (1) and would like to make some comments.

Based on the physical examination findings, we are inclined to think that the patient suffered from Klippel-Trenaunay syndrome. These patients are characterized by the presence of a "port wine" hemangioma on either the neck, trunk, or upper or lower extremities that is associated with spinal cord arteriovenous malformations (2–4). Varicose veins, bone, and soft tissue hypertrophy may also be present.

As mentioned by the author, these cord lesions may bleed spontaneously after straining or coughing. In fact, 80% or more of these angiomas spontaneously bleed at some time during the life of the patient (2). This occurrence is due to loss of autoregulation in the arterial "feeders" of the tumor, resulting in pressure directly transmitted to the abnormally thin-walled vessels that connect the arterial and venous side, thus causing hemorrhage. In about 90% of the cases, bleeding is contained within the lesion, and no neurologic deficit occurs (3). Yet, the incidence of rebleeding is high even in the absence of hypertension (3).

The author contends that the insertion of the epidural catheter primed by increased luminal pressure produced by both the ligation of venous drainage from the area and severe coughing resulted in bleeding of the lesion. Although we agree that peridural techniques are contraindicated in patients with Klippel-Trenaunay syndrome (4), we theorize that in this case it may have occurred even if an epidural catheter would have never been placed owing to the time-course of the events. Assuming that injury to the lesion occurred on insertion of the catheter, we question why the neurologic deficit appeared 30 min after completion of the case. Assuming that the operation lasted 90 min, that would total 2 h after the insertion of the catheter. We would have expected neurologic signs to appear earlier, especially in a patient who received heparin in the early part of the case.

Perhaps, the patient had a bleeding episode before surgery, and the coughing, straining, and sudden increases of blood pressure produced further bleeding and the epidural hematoma.

Additionally, we would like to point out that hypovolemia may precipitate thrombocytopenia, hypofibrinogenemia, elevated levels of fibrinopeptide A, and fibrinogen degradation products in some patients with large hemangiomas (Kasaback-Merritt syndrome). These patients may progress to disseminated intravascular coagulation that responds only to tumor resection (5,6). As this is usually not feasible, maintenance of adequate intravascular volume and normal hemodynamics is most important in patients with Klippel-Trenaunay syndrome.

Finally, we suggest that removal of epidural catheters in patients who have received heparin be withheld until one has documented a normal partial thromboplastin time. We are currently conducting a study in patients who needed full heparinization while the epidural catheter was in place. In 18 patients, we have not seen the development of epidural hematomas despite a mean heparinization time of 2 wk. We discontinue the catheter once heparin is switched to coumadin and the partial thromboplastin time returns to normal.

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In Response:

The hemangioma over the clavicular area of the patient I reported was made up of tortuous, distended veins and was not a "port wine" arteriolized capillary type as reported in the Klippel-Trenaunay-Weber syndrome, the anesthetic management of which was reported by de Leon-Casasola and Lema (1). A similar venous plexus was found at surgery in the cervical epidural area. No elephantiasis of the arm or musculoskeletal hypertrophy were present as is frequently found in this syndrome.

It is my impression that an enlarged vein was injured during catheter placement, but no significant bleeding occurred until after surgery when the patient coughed vigorously and the symptoms of epidural pressure rapidly progressed. Although the hematology consultant found no abnormal clotting studies, this was done after the epidural catheter had been removed.

I thank Drs. de Leon-Casasola and Lema for their comments and agree that a partial thromboplastin time measurement after heparin therapy before removal of the epidural catheter is wise. I also agree that epidural anesthesia is contraindicated if *any* type of hemangioma is identified in the same dermatome.

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Reference

1. De Leon-Casasola OA, Lema MJ. Anesthesia for patients with Sturge-Weber disease and Klippel-Trenaunay syndrome. J Clin Anesth 1991;3:409–13.

Insulation of Heated Wire Circuits

To the Editor:

Mizutani et al. (1) recently recommended that insulating the inspiratory limb of the servo-controlled ventilation tubing with orthopedic felt can improve the performance of the servo-controlled heated humidifier. At our institution we currently are using the Marquest SCT2000 heated humidifier with 48-in disposable *heated wire* breathing circuit. We have often experienced the problem of low-temperature alarming owing to cool air from the vents and air-conditioners blowing directly on the circuit. A caution label attached to each circuit supplied by Marquest reads as follows: CAUTION: Do not place material on or around the heated wire circuit. Objects such as pillows, towels, blankets, sheets, drapes, or heavy tape may overinsulate the circuit, impede normal heat convection, and cause damage to the circuit or interruption of treatment.

Recently, when a Marquest heated wire circuit had been wrapped with a disposable paper towel because of persistent low-temperature alarming, melt-down of the corrugated tubing resulted beneath the insulated portion of the tubing. This leak was discovered when the low minute ventilation alarm sounded and the circuit was removed (see Figures 1 and 2).

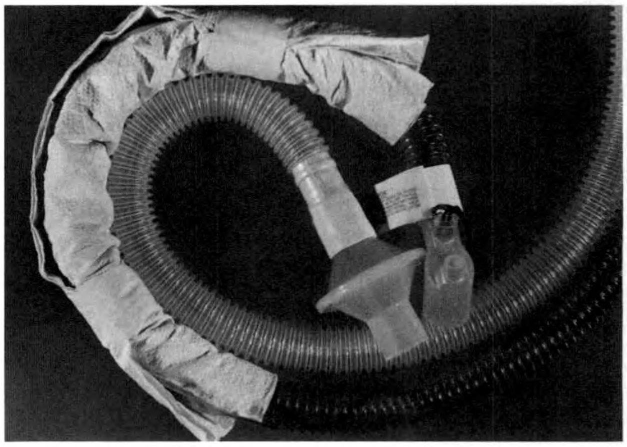

Figure 1. Heated wire circuit insulated with disposable paper towel.

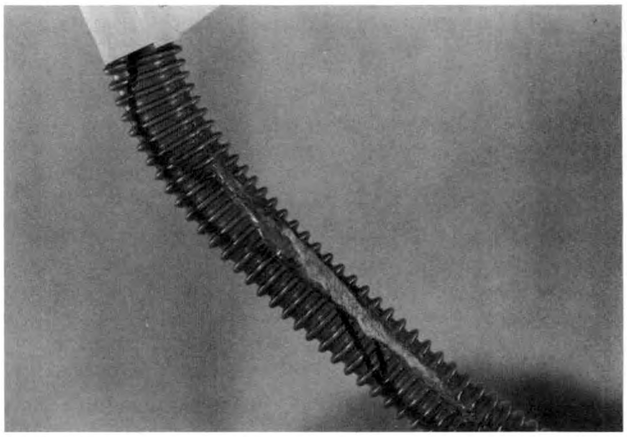

Figure 2. Melted circuit beneath towel.

Although the insulating of ventilation hoses can economically improve the performance of the servo-controlled heated humidifier as demonstrated by Dr. Mizutani, it can also result in tubing melt-down if a heated wire circuit is in use.

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Reference

1. Mizutani AR, Ozaki G, Rusk R. Insulated circuit hose improves heated humidifier performance in anesthesia ventilation circuits. Anesth Analg 1991;72:566–7.

In Response:

The insulation of circuit hoses with heated wire circuits may introduce problems as noted by Wood et al. The application of insulating material to breathing circuits was recommended as an economical *substitute* for heated wire systems, thereby eliminating the need and expense of heated wires (1). We agree that these two methods of maintaining circuit heat should not be used simultaneously.

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1. Mizutani AR, Ozaki G, Rusk R. Insulated circuit hose improves heated humidifier performance in anesthesia ventilation circuits. Anesth Analg 1991;72:566–7.

Endrate or Amidate Again

To the Editor:

We read the letter by Dr. Murphy (1) regarding edetate disodium (Endrate, Abbott Laboratories, North Chicago, Ill.) and etomidate (Amidate, Abbott Laboratories) with interest. We also have experienced several incidences of confusion with etomidate and edetate disodium. On two occasions, resident anesthesiologists received Endrate instead of the 20-mL size of Amidate. One incident was the result of an Endrate 20-mL ampule being incorrectly placed in the 20-mL Amidate box in the operating room pharmacy. A standard practice is to arrange pharmacy stock in alphabetical order by generic name. Thus, these items can be easily misplaced. To decrease this error, we decided to provide Amidate as the 10-mL ampule. Another incident occurred when an anesthesiologist picked up an ampule from the pharmacy counter and shortly returned with the Endrate and said "This is not what I want." On August 23, 1990, we sent a request to Abbott Laboratories to examine their labeling of these products to help minimize the similarity of appearance. Their written response of October 8, 1990 (personal communication) stated that no labeling changes were planned. Although Abbott does comply with Food and Drug Administration labeling requirements and it is every practitioner's responsibility to double-check product labels, we believed their inaction was insensitive to the realities of practice.

The pharmaceutical industry and pharmacy buying groups should become more sympathetic to the potential for human error. Mere color coding instills a false sense of security. We need labels that are clear and easy to read when placed on ampules and vials. Similar-appearing and similar-sounding items must be readily distinguishable. Although uniform labels may work well for soup, pharmaceutical labeling should emphasize the product rather than a corporate identity.

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1. Murphy JL. Endrate or Amidate. Anesth Analg 1991;73:237.

Alterations to the Patil-Syracuse Mask for Fiberoptic Intubation

To the Editor:

In a recent letter, Williams et al. (1) reported the risk of carrying part of the silicone membrane used with the Patil-Syracuse (P-S) mask into the patient's trachea during fiberoptic intubation. A similar complication was reported by Zornow and Mitchell in 1986 (2). At my facility, I have difficulty maintaining a stock of the silicone membranes for the P-S mask and have found that they are relatively expensive, costing almost twice the price of an endotracheal tube (ETT). In addition, when a cuffed ETT is pushed through the diaphragm, the diaphragm frequently ruptures as the cuff passes through the hole in the diaphragm. Therefore, I have devised the following guidelines when using the P-S mask:

1. Only noncuffed ETTs are used with the silicone diaphragm. This generally means a 5.0 ETT, although a well-lubricated 6.0 ETT can pass through the silicone diaphragm without tearing the diaphragm.
2. For larger ETTs with cuffs, a disposable diaphragm is fashioned by cutting off the entire length of the little finger of a nonsterile rubber glove. This "condom" is pulled over the mask opening for the fiberscope and a 3- or 4-mm-long slit is cut in the tautly stretched rubber with a needle. A warmed and lubricated ETT is gently inserted through the diaphragm as the rubber is allowed to relax around the ETT. This mask-diaphragm-ETT assembly is then placed over the patient's mouth with the ETT directed into an in-place oral airway. When the fiberscope has been directed into the trachea and the ETT is ready to be advanced, the rubber diaphragm is *cut away* and removed so as to ensure that none of it is carried into the airway.

There are numerous variations of the P-S mask possible with any variation of a T-tube that will fit a mask and a circuit, e.g., a "peep-saver" or in-circuit oximeter connector (3). I am aware of two commercial products that address this problem, but thus far I have been unable to find them in the United States (4,5). Perhaps in the future a more durable and less expensive diaphragm for the P-S mask will be available here. But for the time being, whenever I use the P-S mask with either the silicone diaphragm or one of my own making, I check the diaphragm before advancing the ETT to ensure that all parts of it can be accounted for.

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An Alternative Diaphragm for Patil-Syracuse Masks

To the Editor:

Williams and colleagues (1) present a case of a potential airway foreign body resulting from use of a Patil-Syracuse mask. The foreign body resulted owing to rupture of the rubber diaphragm through which the bronchoscope and endotracheal tube are passed during endotracheal intubation.

During my use of a Patil-Syracuse mask, the diaphragm also ruptured and created rubber fragments that potentially could have been introduced into the patient's airway. Fortunately, the defect was noticed and introduction of a foreign body did not occur. As stated, the diaphragms are made of very thin, weak rubber that tears easily. The diaphragm may allow passage of a small bronchoscope, but a large bronchoscope or endotracheal tube would likely often rupture the diaphragm.

To solve this problem, I have been making a diaphragm out of material from a latex surgeon's glove. The procedure to make the diaphragm is described below (Figure 1).

1. Place two layers of rubber glove over port of mask
2. Secure rubber over port of mask by tying cotton umbilical tape or heavy suture around port, leaving rubber taut but not overstretched
3. Cut excess rubber away from port, leaving 2–3-mm margin
4. Cut a cross-shaped incision through diaphragm, each approximately 5 mm long
5. Lubricate diaphragm well before using

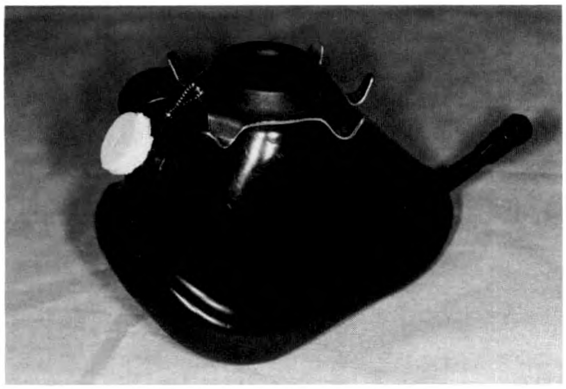

Figure 1.

Any size bronchoscope and up to an 8-mm endotracheal tube can pass through this diaphragm without difficulty. Occasionally the cuts in the diaphragm have torn slightly, but inspection after use suggests that no rubber fragments have ever ruptured from the diaphragm.

I too find the Patil-Syracuse mask to be a very valuable aid in fiberoptic intubation (1–3). Having a patient well anesthetized with an inhaled anesthetic throughout the intubation procedure makes teaching fiberoptic intubation less stressful on the patient as well as the anesthesia team.

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The views expressed in this letter are those of the author and do not reflect the official policy of the Department of the Army, Department of Defense, or the United States Government.

Antiemetic or Antinauseant Effect of Ondansetron?

To the Editor:

The recent papers on the antiemetic action of ondansetron (1,2), with the accompanying editorial (3), highlights one of the major pharmacologic advances in recent years. No longer practicing in anesthesiology, we have had considerable experience with ondansetron in oncology where drug-induced sickness is a very major problem, particularly cisplatin. Here the benefits of ondansetron are such that it has been said that "the days when patients refuse cancer therapy because of the severity of drug-induced nausea and vomiting should be over" (4). We have found it to be the only drug that will terminate an actual emetic episode, in comparison with the prophylactic effect of the older antiemetics.

However, two of our findings could be of interest to anesthesiologists. Ondansetron is much more effective in preventing vomiting than in reducing nausea. This may not be as major a problem in the postoperative period as after chemotherapy, when it can persist for several days. In this situation we have found stimulation of the P6 acupuncture point to be a valuable adjuvant to ondansetron (5,6), and this may be helpful in the postoperative period. We have a strong clinical impression that ondansetron is particularly effective against sickness from opioids: this could be very useful in anesthesia practice where much of the sickness can be due to such drugs.

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Epidural Kits: Incompatible Contents

To the Editor:

Recently in this department we have begun to use Perifix continuous epidural anesthesia kits (Burron Medical, Inc.) for the relief of pain during labor. On two occasions, using this kit and a loss of resistance technique to identify the extradural space, there was loss of resistance as soon as the glass syringe was attached to the Tuohy needle. This loss of resistance remained despite advancing the Tuohy needle into the interspinous ligaments. On both occasions, the needles were withdrawn and retained for inspection. The epidural was carried out using a new Tuohy needle and syringe.

After examining both the syringes and needles, it was found that the syringe maintained constant pressure when tested against a finger pulp. However, the plastic hub of the Tuohy needle was noticed to be cracked (Figure 1). When these syringes and needles were tested as a unit against a constant pressure, loss of resistance occurred in the syringe owing to an air leak from the cracked hub. These cracks presumably occurred during the extradural block when the metal tip of the syringe is fitted into the plastic hub of the Tuohy needle, metal being stronger than the plastic. This problem may be avoided by using either plastic-tipped syringes or metal-hubbed needles in these kits.

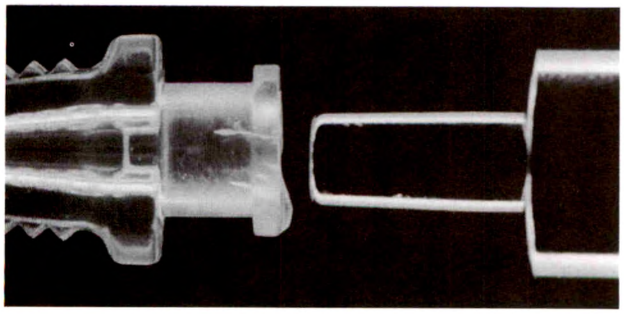

Figure 1. The metal tip of the syringe is shown aligned next to the cracked plastic hub of the Tuohy needle.

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Unusual Complication of Tracheal Intubation

To the Editor:

We report a case of defect of an endotracheal tube (ETT)-induced ventilatory leakage, undetected by preinduction checking. The No. 34 Rush ETT was routinely checked before thyroidectomy under general anesthesia: the cuff was inflated for 20 min without evidence of air leakage. The flexible ETT was a latex-armored tube. An air leak became apparent during surgery after 20 min of controlled respiration through the orotracheal tube. The pilot balloon was noticed to be deflated, and regular inflation of the cuff was necessary during the termination of the procedure. After extubation of the patient's trachea, the ETT was checked and the cuff was again inflated. With surprise we observed that the cuff and the pilot balloon remained inflated! A defect on the pilot balloon line was therefore suspected. We slightly stretched the ETT. At that time the cuff and the pilot balloon spontaneously deflated. A small puncture was found on the pilot balloon line (Figure 1). This very unusual complication of an ETT became apparent only when the surgeon applied a slight pressure on the neck for the thyroidectomy. The pilot balloon line is rarely involved in complications of tracheal intubation (1,2). Our letter seems to be the first report of a leak of the pilot balloon line that could not be detected by the usual preanesthetic checks.

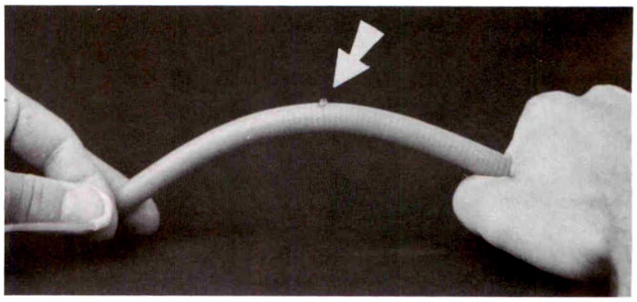

Figure 1. The balloon line is filled with air and water. A bubble is trapped on the leak when the endotracheal tube is bent.

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Alcohol After Midazolam Sedation

To the Editor:

I found the article by Lichtor et al. (1) a valuable contribution to our knowledge of interaction between sedatives and alcohol. I would, however, raise two points of fact.

First, the units of blood alcohol concentration reported as mg/100 mL were 100 times too low, e.g., 0.56 ± 0.13 should have been 56 ± 13 (which is the same as 12.2 ± 2.8 mmol/L).

Second, the alcohol concentrations and equivalents of the various beverages, beer, wine, and spirits, seem a little odd to this frequent visitor to the United States. Given the ratio of volumes, i.e., 1.4 L of beer, 950 mL of wine, and 180 mL of hard liquor, and assuming hard liquor to be 40% alcohol (a fairly universal standard), we can deduce that beer should contain 5.14% alcohol and wine 7.5%. I have never been able to obtain American beer as strong as that (more's the pity), and a quick perusal of 12 different bottles of California wine on my local wine merchant's shelves showed an alcohol content varying from 12% to 13%. I doubt if many of your readers would equate 1.4 L of beer (about four cans) with a quarter of a bottle of bourbon, let alone 1.3 bottles of wine!

Otherwise I enjoyed the paper.

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Pain Upon Injection in the Epidural Space: Common and Unexplained

To the Editor:

Miguel et al. (1) recently reported a case of multiradicular pain associated with epidural injection and suggested that this side effect had not been previously reported in the literature. There is no doubt, however, that sharp, acute pain on injection in the epidural space is well recognized, if not satisfactorily explained.

Pain or discomfort can occur on injection of less than 20 mL in the lumbar epidural space, during epidural blood patch (2). In 1983, Crawford et al. (3) reported results from a multicenter study on long-term epidural treatment with transcutaneous epidural catheters. They recognized the importance of pain on injection and stated that "Reasons for removing an extradural catheter were injection-related pain, ..." Arner et al. (4), in a nationwide survey in Sweden concluded that among other technical problems, ". . . injection pain was an obstacle to successful treatment." Olsson et al. (5) mentioned pain on injection in an overview stressing the importance of preoperative and postoperative teaching of the patient and the family. Liew and Hui (6) in a series of 252 cancer pain patients, mostly with bone metastasis, stated that "the major drawbacks were catheter failure which required reinsertion, and sharp pain during injection in the later stages of therapy." Recently, Plummer et al. (7) showed on a retrospective study of 313 patients that more than 12% of patients experienced pain on epidural injection. This was the most frequent side effect encountered and led to the removal of the catheter in some patients. Our own experience with more than 100 patients with implanted epidural catheters certainly confirms that pain on injection is a common problem, regardless of the level of insertion of the catheter.

Pain on injection in the epidural space comes as no surprise for clinicians with experience in long-term spinal opiate administration. The nature of the pain ranges from a dull, ill-localized discomfort to an excruciating unilateral or bilateral radicular pain. Decreasing the rate of injection and/or the volume of the bolus dose can solve the problem satisfactorily in most but not all patients. It should be mentioned that not infrequently, the pain on injection spontaneously decreases or even disappears after a few days or weeks.

The mechanism that causes pain on injection in the epidural space is essentially unknown. Irritant solution (alcohol or phenol) as well as high doses (or concentrations) of morphine can cause pain in animals (8) and humans (9). On the other hand, pain seems consistently related to either the volume or the pressure of the injection, or both, and might therefore involve an altered compliance of the epidural space. Although pain on injection might be more frequent with the occurrence of epidural metastasis, previous spinal radiotherapy, vertebral collapse, or when the catheter has been in place for longer periods (usually more than 6–8 mo), no convincing correlation has been demonstrated. Although fibrosis is known to occur in the epidural space after long-term use of an epidural catheter, these changes are usually minor and of questionable clinical relevance.

In conclusion, we wonder whether or not Miguel et al. have described an entity that is different from a long known and often reported phenomenon. If an altered compliance results in a painful compression (or dilatation), it seems irrelevant whether air or liquid is injected. We therefore believe that Miguel et al.'s observation cannot be considered as *princeps*, and that it is, at best, a trivial variation of a common and previously reported side effect of injection in the epidural space.

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In Response:

We appreciate Dr. Buchser and Chédel's time and effort to raise some interesting observations. However, we caution them in possibly missing the point. The acute volume change produced by the injection of fluid into the epidural space at any level certainly has the potential to produce discomfort and a radicular syndrome. The etiology of that pain is somewhat nebulous. Our main postulate in the publication was that loculated air in the epidural space effectively decreased the volume of an already anatomically smaller epidural space, thereby predisposing to the development of the multiradicular syndrome. That the pain syndrome elicited was multiradicular in symptomatology further underscored air as an etiologic factor, as air could be found along the corresponding dermatomal segments to the multiradiculopathy. As air had not been previously identified as an etiologic factor in the genesis of epidural injection pain, the finding certainly surpasses the "trivial." Therefore, we believe when the epidural space is being localized, especially in the smaller cervicothoracic segments, preservative-free water or saline should be considered in place of air to prevent the development of a volume-induced multiradicular pain syndrome.

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Ranitidine Does Not Have a Uniquely Lower Affinity for Cerebral H_2-Receptors

To the Editor:

In a recent paper, Audibert et al. (1) erroneously conclude that ranitidine differs from other H_2-receptor antagonists in its effect on modulating hypoxia-induced increases in cerebral blood flow. This conclusion was based on false assumptions concerning the relative potency of ranitidine, famotidine, and roxatidine for blocking gastric H_2-receptors.

The literature, including the references cited by Audibert et al., indicates that famotidine is 4–10 times more potent than ranitidine and that roxatidine is twice as potent as ranitidine (2–5). Although equipotent doses of famotidine (0.4 mg/kg) and roxatidine (1 mg/kg) were examined, they were not directly compared with an equipotent dose of ranitidine (2 mg/kg). Instead, they were compared to 1 mg/kg ranitidine, which is at best half as potent in blocking H_2-receptors. Not surprisingly, this dose of ranitidine did not exert comparable pharmacologic effects. However, when Audibert et al. examined the effects of an equipotent dose of ranitidine (2 mg/kg) in three additional dogs (described by the misnomer "double-dose"), the effects on cerebral blood flow were comparable to those observed with famotidine and roxatidine.

These results support a physiologic role for histamine interaction with H_2-receptors in the modulation of cerebral blood flow (6); the ability of equipotent doses of various H_2-blockers to equivalently inhibit hypoxia-induced increases in cerebral blood flow does not support the hypothesis that ranitidine has a uniquely lower affinity for cerebral H_2-receptors. Rather, these results confirm that, in general, ranitidine is less potent than famotidine or nizatidine.

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In Response:

In our early experiments with H_2-receptor blocking agents we used 4 mg/kg IV cimetidine in the dog. This dose inhibited the hypoxia-induced increase in cerebral blood flow (1). To test other H_2-blockers with equipotent doses, we referred to the human data in the literature about the maintenance of gastric pH above 4, by IV treatment. These doses were 300 mg for cimetidine and 50 mg for ranitidine, that means for an adult of 60 kg an IV dose of 5 mg/kg and

0.8 mg/kg, respectively (2). In the same way, the review article by Feldman and Burton (3), published after our article in *Anesthesia & Analgesia* was accepted, gives a relative potency of ranitidine 4–10 times that of cimetidine. Thus the dosage of H_2-receptor antagonists used in our experiment was approximately equipotent according to data obtained in humans. It remains speculative if this assumption holds true in dogs. Nevertheless, our results show that the dose of ranitidine effective on the cerebral blood flow in hypoxia was not 1 mg/kg but 2 mg/kg IV.

We thank Dr. Berger for emphasizing the important role of histamine in cerebral vasodilation during hypoxia. We wish to add that in dogs the cerebral vasodilation during hypercapnia is not modified by cimetidine IV at the dose of 4 mg/kg (4).

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Long-Distance Anesthesia

To the Editor:

This technique was originally developed for facial cosmetic surgery, primarily for facelifts. However, we now utilize it for a wide variety of plastic surgery procedures including bilateral TRAM flap breast reconstruction and craniofacial operations. It has been used over the past 5 yr in more than 400 patients without a serious incident.

We relate our experience because of the uniform disbelief expressed by anesthesiologists during the travels of our chief of plastic surgery (Luis O. Vasconez, MD) as visiting professor. The anesthetist or anesthesiologist along with the anesthesia machine, monitors, and other anesthesia equipment are located near the patient's feet. During induction, the attending anesthesiologist stands near the anesthesia machine while the anesthetist or resident stands at the patient's head. A reinforced endotracheal tube is utilized and is sutured to the tongue with 2-0 silk by the plastic surgeon. Neither postoperative pain nor bleeding have been a problem from this suture. The anesthesia breathing tubes are doubled in length by adding an equal length of corrugated extension tubing, which is purchased in 100-foot rolls. The extension tubings are connected to the anesthesia circuit with two double-sided 22-mm male adapters (e.g., Bird male adapters No. 395220). The connections are wrapped several times with tape to prevent leaks and disconnects. Recently, however, we have become aware of 120-in anesthesia circuits and have placed an order from Critical Systems, product No. 81203B-06. This alternative may be even safer with fewer potential disconnect sites. However, we have not had any episodes of disconnect to date. In addition, it may be cost-effective particularly when anesthetist assembly time is considered.

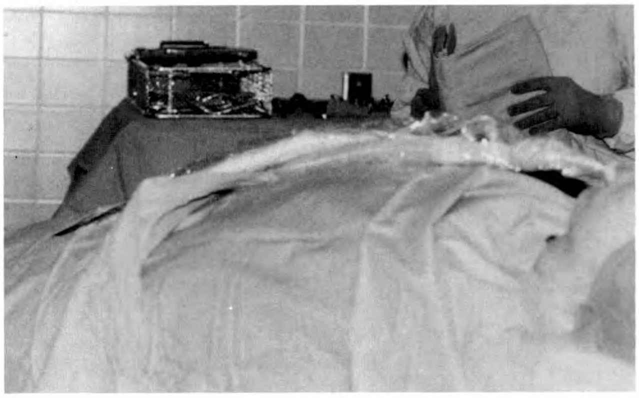

Figure 1.

Many anesthetists have asked about an increase in dead space. However, the only true dead space is that between the Y-connector and the endotracheal tube.

After the surgical preparation, the anesthetic circuit and Y-connector are covered with 42 × 24-in Vi drape (nonsticky) regular surgical film (Bectin Dickinson Acute Care Division, catalog No. 37-1053-1) (Figure 1). The patient is draped as desired for the surgical procedure. The surgeon and many assistants have complete access to the patient's head. In addition, the anesthetist usually has an unobstructed view of the patient's face, rarely possible when utilizing other positions such as in back of the head or to the side of the patient as used by our other head and neck surgeons.

Although originally described nearly 15 yr ago for plastic surgery of the head and neck (1), this position has not gained popularity. With current standards for anesthesia machines (2) as well as monitoring standards including pulse oximetry and capnography, we have found this position to be both safe and extremely beneficial to the surgeon. The patient in turn benefits from an improved cosmetic look.

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Book Reviews

A Rational Basis for Anesthesia

G. Dal Santo. Padua, Italy: Piccin Nuova Libraria, 1990, 933 pp.

This book constitutes the effort of a single author to transcribe his many years of clinical teaching and lecturing into a single large treatise of "textbook and reference dimensions." The author states his aim as being the presentation of the principles of anesthesiology that are "well-proven and accepted. . .and that apply to the daily practice of anesthesia." Even so, he has written some 900 pages, obviously a considerable effort for a single author.

The book is organized around a series of well-chosen topics of direct clinical interest. These include the concept of anesthesia; properties, mechanisms of action, and effects of anesthetic agents; techniques for anesthetic administration; techniques for monitoring the effects of anesthetic agents; and finally, a series of chapters on conditions that may affect the anesthetized patient, including age, pregnancy, patient positioning, and immunologic reactions. One gains the impression that each chapter was an independent lecture, intended for medical students or fledgling anesthesia residents. There is considerable factual information, coupled with abundant illustrations and diagrams, but almost all of the references and figures are at least 5–10 years old. In particular, the chapters dealing with the molecular basis of anesthetic action are seriously outdated, and one must look elsewhere for current information on neurotransmitters in relation to anesthetic action. On the other hand, the chapters on pharmacokinetics, chemical and physical principles, and patient positioning deal with well-established concepts, clearly presented and easy for the novice to understand and apply. The layout of this section and most of the book as well resembles Adriani's *Chemistry and Physics of Anesthesia* in terms of printing style and placement of figures and illustrations. The book, as a whole, is easy to read rapidly, but the writing style is hobbled by an excessively formal and redundant format that occasionally interferes with clarity.

A Rational Basis for Anesthesia is a repository of useful basic information. It is probably best directed at the level of the medical student or beginning resident who needs a well-delineated, dogmatic presentation of information. One will not find the latest developments in these pages. The subject matter is confined to what is tried and true and does not venture into uncharted waters. On the other hand, as Dal Santo stated in the preface, it does provide the newcomer and experienced practitioner with a presentation of basic concepts of anesthesiology, clearly and unambiguously presented.

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Drug Infusions in Anesthesiology

Robert J. Fragen, ed. New York: Raven Press, 1991, 226 pp, $82.00.

The development of new drugs that are short-acting, potent, rapidly metabolized, and readily cleared has resulted in renewed interest in the use of infusions in anesthesia today. This new text deals with this rapidly expanding area of anesthesia in the appropriate detail. The introduction of agents such as propofol, alfentanyl, esmolol, and atracurium, which necessitate tailored methods of administration to optimize their effects, makes this book both topical and practical for current anesthesiologists. In addition, the demand for rapid complete recovery from anesthesia by day surgery units and patients wanting shorter hospital stays has heightened the interest in intravenous anesthesia achieved by the infusion of short-acting agents.

Drug Infusions in Anesthesiology is divided into eight chapters supplemented by a practical appendix of drugs suitable for administration by infusion. The listing of loading doses, infusion rates, and plasma concentrations can be useful to the practicing anesthesiologist. In the general text, there are chapters on the theoretical principles of administering drugs by infusion and the various pumps and systems available for achieving this type of anesthesia. Specific chapters deal with infusing intravenous anesthetics, opioids, muscle relaxants, and vasoactive agents. The topics of total intravenous anesthesia and postoperative analgesic infusions receive special consideration.

The chapters are authored by experts from Northwestern and Duke Universities, and reflect the extensive knowledge of the subject available in those centers. Dr. Fragen has ensured that the style is consistent and the chapters are well written and very readable. Although the book is concise (226 pages), the subject is thoroughly covered with no obvious omissions or oversights. The chapters dealing with the various drug groups suitable for infusion are both complete and clinically relevant. The section on pumps and systems is especially practical. It is an excellent review of the current state of knowledge and technology and will be

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of use to anesthesiologists wanting an understanding of the mechanics and mechanisms of infusion systems.

If anything, this book is too thorough. It attempts to cover all possible infusions used in anesthesia rather than intravenous anesthesia and analgesia. This detracts somewhat from the perceived focus of the book.

Is this an essential textbook? It is probably not necessary for all anesthesiologists and anesthesia residents. It should be available in all departmental and hospital libraries as a very good reference source on this new topic, which will become more central to the practice of anesthesia in the next few years. This reviewer plans to have a copy in his own library.

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The Culture of Pain

David B. Morris. Berkeley: University of California Press, 1991, 342 pp, $29.95.

> When you feel pain in a leg that has been amputated, where is the pain? If you say it is in your head, would it be in your head if the leg had not been amputated? If you say yes, then what reason have you ever for thinking you have a leg?
>
> Bertrand Russell

The Culture of Pain is a unique book. The author, who is a Professor of English, takes the reader on a most eclectic tour of pain . . . not in the clinical sense, but in the critical sense. By juxtaposition of literary quotation, visual art, and theological viewpoint, Professor Morris has crafted a most entertaining and thought-provoking book. Chapter titles range from "The Pain of Comedy" to "The Uses of Pain" to a chapter entitled, "Sex, Pain and the Marquis de Sade." Each chapter is made up of loosely related essays that present an exploration of pain's history in Western literature and culture from a variety of viewpoints. The use of graphic arts and sculpture to reinforce the written word makes the book immensely readable. For the pain specialist who enjoys literature and the arts, this book will provide a pleasant respite from the traditional medical textbook format.

Steven D. Waldman, MD
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The Effects of Anesthetics Upon Cerebral Circulation and Metabolism. Experimental and Clinical Studies

J. B. Madsen and G. E. Gold, eds. New York: Springer-Verlag, 1990, 160 pp, $49.00.

This book is primarily addressed to neuroanesthesiologists and, therefore, omits an overview of the physiology of cerebral circulation and metabolism. The book focuses on a review of the effects of anesthetics and anesthesia-related drugs on cerebral circulation and metabolism. In that sense, the book is unique.

The book consists of 10 chapters including a brief chapter on general considerations and a general summary. Chapter 2 reviews inhaled anesthetics thoroughly and summarizes the voluminous results reported in the literature by dividing them into experimental studies and human investigations. This reviewer especially appreciated the conclusions presented concerning the effects of halothane, enflurane, and isoflurane.

The effects of hypnotic drugs are, in general, well summarized. However, the discussion of the effects of althesin and etomidate was excessive, involving five of the 14 figures in the book, and the legends for these figures were long and repetitious. Concept was sacrificed for detail.

In the chapter reviewing the effects of centrally acting analgesics (morphine, fentanyl, sufentanil, and alfentanil) and narcotic antagonists (naloxone), this reviewer would have preferred to see more discussion concerning whether sufentanil or alfentanil is superior to fentanyl for neurosurgical anesthesia.

The summary discussion of the effects of neuromuscular blocking agents suggested that most of the commonly used drugs have minimal effects on intracranial hemodynamics and metabolism despite the reports of adverse effects (seizures, ICP elevation) with some of these drugs or their metabolites in animal experiments.

In the sixth chapter, the authors thoughtfully discuss the effects of lidocaine, mannitol, and furosemide. One point that is not easily accepted is the authors' statement that the risks of rebound phenomenon indicate that mannitol primarily should be used in a single dose in connection with acute ICP increases (page 57). Chapter 7 summarizes well the effects on intracranial hemodynamics of drugs used for controlled hypotension. Drawbacks in this chapter include inconsistent use of abbreviations and several typographical errors.

Chapter 8 is a summary of the clinical investigations performed during craniotomy in the authors' own institution. Although the authors have made numerous contributions to the understanding of neuroanesthesia, this chapter is somewhat superfluous because the results had already been presented and discussed. In the ninth chapter cardiovascular effects and cerebrovascular and spinal cord dynamics are succinctly and thoughtfully summarized, especially the problems associated with the sitting position. Finally, the book is well referenced with 50 pages devoted to primarily current references.

In summary, despite some unnecessary repetition and somewhat disappointing figures, this reviewer believes that this book is useful to anesthesiologists working in neuroanesthesia. The book also points out what is still unknown or controversial and in need of further study to improve the anesthetic management of neurosurgical patients.

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Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Gal RA. *A Glance at Transesophageal Echocardiography*. New York: Churchill-Livingstone, 1992, Videotape and Manual.

Lerman J, ed. *New Developments in Pediatric Anesthesia*. Volume 9, No. 4 of Anesthesia Clinics of North America. Philadelphia: W.B. Saunders, 1991, 219 pp, $74.00 annual subscription or $32.00 single issue.

Morgan GE, Mikhail MS. *Clinical Anesthesiology*. Norwalk, Conn.: Appleton & Lange, 1992, 747 pp, $39.95.

Ostheimer GW, ed. *Manual of Obstetric Anesthesia*. 2nd ed. New York: Churchill Livingstone, 1992, 468 pp, $55.00.

Rogers MC, ed. *Current Practice in Anesthesiology*. 2nd ed. St. Louis: Mosby Year Book, 1990, 536 pp, $79.00.

Short CE, Van Poznak A, ed. *Animal Pain*. New York: Churchill-Livingstone, 1992, 587 pp, $84.95.

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Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it.
WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.
PRECAUTIONS: General: Limited data on histamine assay and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.
Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.
Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.
Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.
Long-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPHERAL NERVE STIMULATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTENT EXCESS DOSING.
Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.
Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.
C.N.S.: Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.
Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.
Inhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.
Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.
Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.
Drug/laboratory test interactions: None known.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.
Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. Norcuron® should be given to a pregnant woman only if clearly needed.
Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.
ADVERSE REACTIONS: Norcuron® was well tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit. (see PRECAUTIONS).

Bronchospasm, flushing, redness, hypotension and tachycardia have been reported in very rare instances.
OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade.
DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.
Use by Continuous Infusion: After an intubating dose of 80-100 µg/kg, a continuous infusion of 1 µg/kg/min can be initiated approximately 20–40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations. (see PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulator. An initial rate of 1 µg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 µg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of nondepolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (µg/kg/min)	Infusion Delivery Rate (mL/kg/min) 0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron® in 100 mL solution
†20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON® INFUSION RATE — mL/MIN

Amount of Drug	Patient Weight – kg						
µg/kg/min	40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, therefore, no dosing recommendation can be made.
COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution	5% glucose in saline
5% glucose in water	Lactated Ringers
Sterile water for injection	

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.
STORAGE: 15-30°C (59-86°F). Protect from light.
AFTER RECONSTITUTION: :
- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

REV. 3/89

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DIPRIVAN®

INJECTION
10 mg/mL
propofol

EMULSION FOR IV ADMINISTRATION

(For full prescribing information, see package insert. A Brief Summary follows.)

CLINICAL PHARMACOLOGY—Individualization of Dosage: General: DIPRIVAN Injection is a potent sedative hypnotic agent which provides clinically useful anesthetic and sedative actions depending upon the dose and technique of administration. Important factors to consider include the types of preinduction and concomitant medications, age, ASA physical classification and level of debilitation of the patient, and ultimately, the dose and rate of administration of DIPRIVAN Injection. Individualization of dose and technique will provide a smooth induction and stable maintenance while reducing potential unwanted side effects. Patients with hypovolemia should have fluid-volume deficits corrected prior to administration of DIPRIVAN Injection. **Induction of Anesthesia:** Most adult patients under 55 years of age and classified ASA I or II require 2.0 to 2.5 mg/kg of DIPRIVAN Injection for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular opioids. For induction, DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia. As with other sedative hypnotic agents, the amount of intravenous opioid and/or benzodiazepine premedication will influence the response of the patient to an induction dose of DIPRIVAN Injection. It is important to be familiar with and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated and ASA III or IV patients. Due to the reduced clearance and higher blood levels, most elderly patients require approximately 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds) of DIPRIVAN Injection for induction of anesthesia according to their condition and responses. A rapid bolus should not be used as this will increase the likelihood of undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction and/or oxygen desaturation. (See DOSAGE AND ADMINISTRATION.) **Maintenance of Anesthesia:** Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections. When administering DIPRIVAN Injection by infusion, it is recommended that syringe pumps or volumetric pumps be used to provide controlled infusion rates. **Continuous Infusion:** DIPRIVAN Injection 100 to 200 μg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction dose higher rates of infusion are generally required (150 to 200 μg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased 30%- 50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) to 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as an opioid, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses. For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile. When supplementation with nitrous oxide is not provided, administration rate(s) of DIPRIVAN Injection and/or opioids should be increased in order to provide adequate anesthesia. Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 50 to 100 μg/kg/min should be achieved during maintenance in order to optimize recovery times. **Intermittent Bolus:** Increments of DIPRIVAN Injection 25 mg (2.5 mL) to 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia. DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and opioid analgesics, as well as with inhalational and regional anesthetic agents. In the elderly, rapid bolus doses should not be used as this will increase cardiorespiratory effects including hypotension, apnea, airway obstruction and/or oxygen desaturation. Most elderly patients require a reduction of the recommended maintenance rates for healthy adults (< 55 years) to 50 to 100 μg/kg/min (3 to 6 mg/kg/h). **MAC SEDATION:** When DIPRIVAN Injection is administered for sedation, rates of administration should be individualized and titrated to clinical response. In most patients the rates of DIPRIVAN Injection administration will be approximately 25% of those used for maintenance of general anesthesia. During initiation of MAC sedation, slow infusion or slow injection techniques are preferable over rapid bolus administration. During maintenance of MAC sedation, a variable rate infusion is preferable over intermittent bolus dose administration. In the elderly, debilitated and ASA III or IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation. (See WARNINGS.) **A rapid bolus injection can result in undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction and/or oxygen desaturation. Initiation of MAC Sedation:** For initiation of sedation, either an infusion or a slow injection method may be utilized while closely monitoring cardiorespiratory function. With the infusion method, sedation may be initiated by infusing DIPRIVAN Injection at 100 to 150 μg/kg/min (6 to 9 mg/kg/h) for a period of 3 to 5 minutes and titrating to the desired level of sedation while closely monitoring respiratory function. With the slow injection method for initiation, patients will require approximately 0.5 mg/kg administered over 3 to 5 minutes and titrated to clinical responses. When DIPRIVAN Injection is administered slowly over 3 to 5 minutes, most patients will be adequately sedated and the peak drug effect can be achieved while minimizing undesirable cardiorespiratory effects occurring at high plasma levels. In the elderly, debilitated, and ASA III or IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation. (See WARNINGS.) The rate of administration should be over 3-5 minutes and the dosage of DIPRIVAN Injection should be reduced to approximately 80% of the adult dosage in these patients according to their condition, responses, and changes in vital signs. (See DOSAGE AND ADMINISTRATION.) **Maintenance of MAC Sedation:** For maintenance of sedation, a variable rate infusion method is preferable over an intermittent bolus dose method. With the variable rate infusion method, patients will generally require maintenance rates of 25 to 75 μg/kg/min (1.5 to 4.5 mg/kg/h) during the first 10 to 15 minutes of sedation maintenance. Infusion rates should subsequently be decreased over time to 25 to 50 μg/kg/min and adjusted to clinical responses. In titrating to clinical effect, allow approximately 2 minutes for onset of peak drug effect. Infusion rates should always be titrated downward in the absence of clinical signs of light sedation until mild responses to stimulation are obtained in order to avoid sedative administration of DIPRIVAN Injection at rates higher than are clinically necessary. If the intermittent bolus dose method is used, increments of DIPRIVAN Injection 10 mg (1.0 mL) or 20 mg (2.0 mL) can be administered and titrated to desired level of sedation. With the intermittent bolus method of sedation maintenance there is the potential for respiratory depression, transient increases in sedation depth, and/or prolongation of recovery. In the elderly, debilitated, and ASA III or IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation. (See WARNINGS.) The rate of administration and the dosage of DIPRIVAN Injection should be reduced to approximately 80% of the adult dosage in these patients according to their condition, responses, and changes in vital signs. (See DOSAGE AND ADMINISTRATION.) DIPRIVAN Injection can be administered as the sole agent for maintenance of MAC sedation during surgical/diagnostic procedures. When DIPRIVAN sedation is supplemented with opioid and/or benzodiazepine medications, these agents increase the sedative and respiratory effects of DIPRIVAN and may also result in a slower recovery profile. (See PRECAUTIONS, Drug Interactions.) **INDICATIONS AND USAGE:** DIPRIVAN Injection is an IV anesthetic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery. DIPRIVAN Injection, when administered IV as directed, can be used to initiate and maintain monitored anesthesia care (MAC) sedation during diagnostic procedures. DIPRIVAN Injection may also be used for MAC sedation in conjunction with local/regional anesthesia in patients undergoing surgical procedures. (See PRECAUTIONS.) DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. (See PRECAUTIONS.) DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. (See PRECAUTIONS.) DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN Injection has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. (See PRECAUTIONS.) DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. (See PRECAUTIONS.) **CONTRAINDICATIONS:** When general anesthesia or sedation is contraindicated or in patients with a known hypersensitivity to DIPRIVAN Injection or its components. **WARNINGS: For general anesthesia or monitored anesthesia care (MAC) sedation, DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure. Patients should be continuously monitored and facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.** In the elderly, debilitated and ASA III or IV patients, rapid (single or repeated) bolus administration should not be used during general anesthesia or MAC sedation in order to minimize undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction and/or oxygen desaturation. MAC sedation patients should be continuously monitored by persons not involved in the conduct of the surgical or diagnostic procedure; oxygen supplementation should be immediately available and provided where clinically indicated; and oxygen saturation should be monitored in all patients. Patients should be continuously monitored for early signs of hypotension, apnea, airway obstruction and/or oxygen desaturation. These cardiorespiratory effects are more likely to occur following rapid initiation (loading) boluses or during supplemental maintenance boluses, especially in the elderly, debilitated and ASA III or IV patients. DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known. **Strict aseptic techniques must always be maintained during handling as DIPRIVAN Injection is a single-use parenteral product and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms. (See DOSAGE AND ADMINISTRATION, Handling Procedures.) Failure to follow aseptic handling procedures may result in microbial contamination causing fever, infection/sepsis and/or other adverse consequences which could lead to life-threatening illness. PRECAUTIONS: General:** A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and ASA III or IV patients. (See CLINICAL PHARMACOLOGY—Individualization of Dosage.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis. The clinical criteria for discharge from the recovery/day surgery area established for each institution should be satisfied before discharge of the patient from the care of the anesthesiologist. When DIPRIVAN Injection is administered to an epileptic patient, there may be a risk of convulsion during the recovery phase. Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous sequelae (phlebitis or thrombosis) have been reported rarely (< 1%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused

minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. Accidental intra-arterial injection has been reported in patients, and other than pain, there were no major sequelae. Perioperative myoclonia, rarely including convulsions and opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered. Clinical features of anaphylaxis, which may include bronchospasm, erythema and hypotension, occur rarely following DIPRIVAN Injection administration, although use of other drugs in most instances makes the relationship to DIPRIVAN Injection unclear. DIPRIVAN Injection has no vagolytic activity and has been associated with reports of bradycardia, occasionally profound. The intravenous administration of anticholinergic agents (eg, atropine or glycopyrrolate) should be considered to modify potential increases in vagal tone due to concomitant agents (eg, succinylcholine) or surgical stimuli. **Neurosurgical Anesthesia:** Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion are prevented by appropriate measures. **Information for Patients:** Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle, or hazardous machinery or signing legal documents may be impaired for some time after general anesthesia or sedation. **Drug Interactions:** The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (eg, morphine, meperidine, and fentanyl) and combinations of opioids and sedatives (eg, benzodiazepines, barbiturates, chloral hydrate, droperidol, etc.). These agents may increase the anesthetic or sedative effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output. During maintenance of anesthesia or sedation, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anesthesia or sedation and may be reduced in the presence of supplemental analgesic agents (eg, nitrous oxide or opioids). The concurrent administration of potent inhalational agents (eg, isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic or sedative and cardiorespiratory effects of DIPRIVAN Injection. DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (eg, succinylcholine and nondepolarizing muscle relaxants). No significant adverse interactions with commonly used premedications or drugs used during anesthesia or sedation (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Animal carcinogenicity studies have not been performed with propofol. In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using *Salmonella* sp) mutation test, gene mutation/gene conversion using *Saccharomyces cerevisiae*, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test. Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days. **Pregnancy Category B:** Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed. **Labor and Delivery:** DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. **Nursing Mothers:** DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. **Pediatric Use:** DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. **ADVERSE REACTIONS:** Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incidence rates. The adverse experience profile from reports of 150 patients in the US/Canadian MAC sedation clinical trials is similar to the profile established with DIPRIVAN Injection during anesthesia (see below). During MAC sedation clinical trials, significant respiratory events included cough, upper airway obstruction, apnea, hypoventilation, and dyspnea. The most common adverse events which occurred in more than 3% of the patients receiving DIPRIVAN Injection for MAC sedation included hypotension, nausea, headache, and injection site pain or hotness. The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 1573 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient. The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency. **Incidence Greater than 1%—All events regardless of causality, derived from clinical trials. Body as a Whole:** Fever. **Cardiovascular:** Hypotension* (see also CLINICAL PHARMACOLOGY), Bradycardia, Hypertension. **Central Nervous System:** Movement*, Headache, Dizziness, Twitching, Bucking/Jerking/Thrashing, Clonic/Myoclonic Movement. **Digestive:** Nausea** (15%), Vomiting*, Abdominal Cramping. **Injection Site:** Burning/Stinging** (10%), Pain** (10%), Tingling/Numbness, Coldness. **Respiratory:** Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY). **Skin and Appendages:** Flushing. Incidence of unmarked events is 1%-3%; *3% to 9%; **10% or greater. **Incidence Less than 1%—Causal Relationship Probable (Adverse events reported only in the literature, not seen in clinical trials, are *italicized*.) Body as a Whole:** Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. **Cardiovascular:** Tachycardia, Premature Ventricular Contractions, Premature Atrial Contractions, Syncope, Abnormal ECG, ST Segment Depression. **Central Nervous System:** Shivering, Somnolence, Hypertonia/Dystonia, Paresthesia, Tremor, Abnormal Dreams, Agitation, Confusion, Delirium, Euphoria, Fatigue, Moaning, Rigidity. **Digestive:** Hypersalivation, Dry Mouth, Swallowing. **Injection Site:** Discomfort, Phlebitis, Hives/Itching, Redness/Discoloration. **Musculoskeletal:** Myalgia. **Respiratory:** Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia. **Skin and Appendages:** Rash, Urticaria. **Special Senses:** Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus. **Urogenital:** Urine Retention, *Green Urine*. **Incidence Less than 1%—Causal Relationship Unknown** (Adverse events reported only in the literature, not seen in clinical trials, are *italicized*.) **Cardiovascular:** Arrhythmia, Bigeminy, Edema, Ventricular Fibrillation, Heart Block, *Myocardial Ischemia*. **Central Nervous System:** Anxiety, Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures, *Opisthotonus*. **Digestive:** Diarrhea. **Respiratory:** Laryngospasm. **Skin and Appendages:** Diaphoresis, Pruritus, *Conjunctival Hyperemia*. **Special Senses:** Ear Pain, *Nystagmus*. **DOSAGE AND ADMINISTRATION:** Dosage and rate of administration should be individualized and titrated to the desired effect according to clinically relevant factors including preinduction and concomitant medications, age, ASA physical classification and level of debilitation of the patient. **The following is abbreviated dosage and administration information which is only intended as a general guide in the use of DIPRIVAN Injection. Prior to administering DIPRIVAN Injection, it is imperative that the physician review and be completely familiar with the specific dosage and administration information detailed in the CLINICAL PHARMACOLOGY—Individualization of Dosage section. In the elderly, debilitated and ASA III or IV patients, rapid bolus doses should not be used in the methods of administration described below. (See WARNINGS.)**

Induction of Anesthesia	Dosage should be individualized and titrated. **Adults*:** Most patients require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). **Elderly, Debilitated and ASA III or IV Patients:** Most patients require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset). For complete dosage information, see CLINICAL PHARMACOLOGY—Individualization of Dosage.
Maintenance of Anesthesia: Infusion	**Variable rate infusion**—titrated to the desired clinical effect. **Adults*:** Most patients require 100 to 200 μg/kg/min (6 to 12 mg/kg/h). **Elderly, Debilitated and ASA III or IV Patients:** Most patients require 50 to 100 μg/kg/min (3 to 6 mg/kg/h).
Maintenance of Anesthesia: Intermittent Bolus	Increments of 25 mg to 50 mg as needed. For complete dosage information, see CLINICAL PHARMACOLOGY—Individualization of Dosage.
Initiation of MAC Sedation	Dosage and rate should be individualized. **Adults*:** Slow infusion or slow injection techniques are preferable over rapid bolus administration. Most patients require an infusion of 100 to 150 μg/kg/min (6 to 9 mg/kg/h) or a slow injection of 0.5 mg/kg over 3 to 5 minutes. **Elderly, Debilitated and ASA III or IV Patients:** Most patients require dosages similar to adults, but must be given as a slow infusion or slow injection and not as a rapid bolus. (See WARNINGS.)
Maintenance of MAC Sedation	Dosage and rate should be titrated to clinical effect. **Adults*:** A variable rate infusion technique is preferable over an intermittent bolus technique. Most patients require an infusion of 25 to 75 μg/kg/min (1.5 to 4.5 mg/kg/h) or incremental bolus doses of 10 mg or 20 mg. **Elderly, Debilitated and ASA III or IV Patients:** Most patients require a 20% reduction of the adult dose. A rapid (single or repeated) bolus dose should not be used. (See WARNINGS.) For complete dosage information, see CLINICAL PHARMACOLOGY—Individualization of Dosage.

*Adults—healthy, less than 55 years of age

Handling Procedures: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. DIPRIVAN Injection must not be administered through a microbiological filter because this could restrict the flow of DIPRIVAN and/or cause the breakdown of the emulsion. Do not use if there is evidence of separation of the phases of the emulsion. **Strict aseptic techniques must always be maintained during handling as DIPRIVAN Injection is a single-use parenteral product and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms. Failure to follow aseptic handling procedures may result in microbial contamination causing fever, infection/sepsis and/or other adverse consequences which could lead to life-threatening illness.** DIPRIVAN Injection should be prepared for use just prior to initiation of each individual anesthetic/sedative procedure. The ampule neck surface or vial rubber stopper should be disinfected using 70% isopropyl alcohol. DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules or vials are opened. When withdrawing DIPRIVAN Injection from vials, a sterile vent spike should be used. The syringe(s) should be labeled with appropriate information including the date and time the ampule or vial was opened. Administration should commence promptly and be completed within 6 hours after the ampules or vials have been opened. DIPRIVAN Injection should be prepared for single patient use only. Any unused portions of DIPRIVAN Injection, reservoirs, dedicated administration tubing and/or solutions containing DIPRIVAN Injection must be discarded at the end of the anesthetic procedure or at 6 hours, whichever occurs sooner. The IV line should be flushed every 6 hours and at the end of the anesthetic procedure to remove residual DIPRIVAN Injection.

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701G/F

CARDIOVASCULAR FELLOWSHIP OPPORTUNITY

The Department of Anesthesiology at the University of New Mexico School of Medicine has openings at the CA-4 level for advanced training in Cardiovascular Anesthesiology beginning July 1992. The fellowship is a 2-year, comprehensive program designed to train the fellow for a career in cardiovascular anesthesiology. Research in cardiovascular physiology and anesthesia, provision of clinical care for complex adult and pediatric cases, participation in conferences, and teaching responsibilities are part of the fellowship experience. Interested individuals should contact Jorge Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico, 2211 Lomas Blvd. NE, Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

730H/L

THE UNIVERSITY OF NEW MEXICO

Department of Anesthesiology has an immediate opening for a Veterans Administration Chief of Service for Anesthesia at the New Mexico Regional Medical Facility (VA Hospital) in Albuquerque. Requirements include proven administrative, teaching, and leadership abilities, academic experience, and board certification. Appointment will be at the Associate Professor level. Qualified candidates should send CV or contact Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas NE, Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

731H/L

THE UNIVERSITY OF NEW MEXICO

Department of Anesthesiology has faculty positions beginning July 1992 for the following: (1) Obstetrical Anesthesia at the Assistant, Associate, or Full Professor levels; (2) Critical Care Medicine at the Assistant or Associate Professor level. It is expected that candidates for CCM positions will have or be eligible for subspecialty certification. Faculty responsibilities include provision of clinical care, teaching, and research. Qualified candidates should send CV or contact Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas NE, Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

732H/L

THE UNIVERSITY OF NEW MEXICO

Department of Anesthesiology has faculty positions at the Instructor, Assistant Professor, and Associate Professor levels beginning July 1992. Responsibilities include teaching of medical students and residents and the provision of clinical care in a busy tertiary referral center. Opportunities to pursue research interest will be provided. Experience in cardiac, obstetric, neurosurgical, and pediatric anesthesia is desirable. Qualified candidates should address inquiries to Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas NE, Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

733H/L

DEPARTMENT OF ANESTHESIOLOGY

St. Louis University School of Medicine is seeking board-qualified or certified full-time faculty to fill newly created positions to meet the needs of the expanding residency program and new expanding hospital facility. Training and interests in the subspecialty areas of pediatrics, cardiovascular, pain, and neuroanesthesia are desirable. These clinical/teacher positions will also promote academic interests and research development. Participation in the residency training program is essential. The university is committed to affirmative action. Inquiries should be directed to John F. Schweiss, MD, Chairman, Department of Anesthesiology, St. Louis University School of Medicine, 3635 Vista Avenue at Grand Boulevard, St. Louis, MO 63110-0250; telephone (314) 577-8750.

772J/C

PEDIATRIC ANESTHESIOLOGY FACULTY

Section of Pediatric Anesthesiology at the University of Michigan Medical School is seeking an additional faculty member. The Section provides anesthesia for a surgical caseload of 6000 cases/year, 50% of which are outpatients. All pediatric surgical sub-

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CLASSIFIED ADS

Anesthesia and Analgesia makes available classified advertising space for those interested in obtaining positions or wishing to announce meetings, postgraduate courses, or other pertinent events. We require that all advertisements be relevant to the practice of anesthesia and analgesia, and we reserve the right to refuse advertisements that are not relevant.

Specifications. Ads should be typewritten on letterhead stationery; the text should be double-spaced, with the title or key phrase typed in capital letters. Enclose two photocopies with each ad. Display space (minimum ¼ page) is available through Pharmaceutical Media, Inc., 440 Park Avenue South, 14th floor, New York, NY 10016, telephone: (212) 685-5010, FAX: (212) 685-6126.

Rates. Ads cost $1.50 per word per insertion, with a minimum of 20 words. Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. There is an additional fee of $18.00 per insertion for box number ads.*

Payment. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. (Make checks payable to Elsevier Science Publishing Company, Inc.)

Deadline. Copy must be received 7 weeks before publication date (i.e., by January 1 for the March issue); multiple-insertion ads are welcome. Ads may run up to 6 months per purchase order/payment. Please specify in which issue(s) your advertisement is to appear.

Send all ad copy, payments, and correspondence to: *Anesthesia and Analgesia*, Classified Ads, Desk Editorial, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

*When responding to a box number ad, include the box number on all correspondence.

specialties are represented, with an active pediatric cardiac surgery program of over 500 cases/year. An expanding pediatric pain program is currently being developed. Candidates should be BE/BC with a fellowship in pediatric anesthesiology. Appointments can be from the Lecturer to the Professor level in either the clinical or academic track, depending on qualifications and experience. Resources are available for faculty to participate in clinical and laboratory research. Interested candidates should apply to Niall Wilton, MD, Chief, Section of Pediatric Anesthesiology, C-4139, Med Inn Bridge, Box 0800, University of Michigan Medical Center, Ann Arbor, MI 48109-0800 (FAX 313-936-9091). The University of Michigan is a nondiscriminatory, Affirmative Action/Equal Opportunity Employer.

778J/I

ILLINOIS

Large, well-established, single-specialty group of anesthesiologists seeks additional BC/BE anesthesiologists. Challenging opportunity for those interested in a broad-based practice. All surgical subspecialties represented with coverage at three hospitals and two day-surgery facilities. Excellent benefits with early partnership. Please send CV to Associated Anesthesiologists, S.C., 5401 North Knoxville, Suite #49, Peoria, IL 64614.

785K/F

LOUISIANA STATE UNIVERSITY MEDICAL CENTER—SHREVEPORT

Faculty positions available for board certified/eligible anesthesiologists. Duties include patient care, resident and student teaching, supervision of CRNAs, research, and administrative responsibilities. Faculty rank and salary commensurate with experience. Please send curriculum vitae and names of three references to D. Richard Davis, II, MD, Associate Professor and Chairman, Department of Anesthesiology, LSU Medical Center-Shreveport, 1501 Kings Highway, Shreveport, LA 71130-3932. We are an Equal Opportunity/Affirmative Action Employer.

788K/D

TWO PEDIATRIC ANESTHESIOLOGISTS

Virginia Coast—needed to join MD/CRNA staff of university-affiliated children's hospital serving a diverse regional population. Fellowship or experience in pediatric anesthesia and board certification or eligibility required. Full spectrum of surgery. Responsibilities include clinical anesthesia and resident/CRNA education and supervision. Superb location on southeastern Virginia coast within easy access to beaches, mountains, and Washington, D.C. Salary commensurate with training and experience, complemented by an excellent benefit package. For more information contact James Mayhew, MD, Pediatric Anesthesiology, Room 315, Children's Hospital of The King's Daughters, 800 West Olney Road, Norfolk, VA 23507. AA/EOE.

821L/E

Immediate positions available for part-time anesthesiologists, Monday through Friday, 7:00 AM to 4:00 PM (no call), to join a group of 18 anesthesiologists and 8 CRNAs in northwestern Indiana, 30 minutes from downtown Chicago. Send curriculum vitae to Box 825L/C.

825L/C

MICHIGAN

Recently trained BE/BC anesthesiologist wanted to join active practice in busy 127-bed hospital. Wide variety of cases. Very friendly atmosphere. Recreationally oriented Lake Michigan community. Competitive salary package with future partnership will wait for right person. Inquiries to: Jeffrey Kommit, DO, P.O. Box 517, Grand Haven, MI 49417.

830L/C

MAINE - NEEDED - ANESTHESIOLOGIST

To join 5-anesthesiologists, 10-CRNA group doing wide range of surgeries at two community hospitals. No open heart. Picturesque central Maine location near lakes, mountains, and ocean. Referral area of 75,000+. Competitive compensation package. Contact Jill Gilbert at (207) 872-1136 or send CV to Waterville Anesthesia Associates, 44 Main Street, Waterville, ME 04901.

828L/C

PRIVATE PRACTICE OPPORTUNITY

For fellowship-trained MDA interested and experienced in acute and chronic pain management. Currently seeing greater than 600 chronic pain patients per month in hospital-based practice. Send CV and three references to Diana Bird, c/o Medaphis, 3212 West End Avenue, Suite 500, Nashville, TN 37203.

837A/F

ANESTHESIOLOGIST WANTED

BC/BE for progressive community hospital in central Massachusetts. Convenient to ski and surf. Competitive salary leading to early partnership. Reply to Box 839A/C.

839A/C

PENNSYLVANIA

Third anesthesiologist needed for 170-bed hospital in city of 50,000 near major university. Six CRNAs. 4000 cases. No open heart, minimal neuro. Must be able to fit into relatively low-stress practice. Send CV to Michael Clark, MD, Director of Anesthesiology, Mercy Hospital, 2500 Seventh Avenue, Altoona, PA 16602-2099.

840A/C

The Department of Anesthesiology at Duke University Medical Center is seeking qualified full-time faculty for positions in the following categories: CHIEF, VA ANESTHESIOLOGY SERVICE—We are seeking an academic faculty candidate to direct a busy, well-established division of the Department and to enhance our growing clinical, teaching, and research programs at the Durham VA Medical Center. This 450-bed university-affiliated VA performs 3300 surgical procedures per year, including 175 cardiac cases, with statewide VA referral of brain tumor surgery, hip and knee replacement, and renal transplantation. The Anesthesiology Service provides care in nine operating rooms, a nine-bed PACU, eight-bed SICU, and a large Pain Clinic. CRITICAL CARE MEDICINE—We are seeking individuals who are ABA certified or board eligible in critical care medicine, for the position of Co-Director, SICU at the Durham VA Medical Center (where a new ICU tower is under construction) and/or as critical care faculty in the SICU at Duke University Medical Center. Faculty will play an essential role in the coordination of care in a multidisciplinary consulting service and in the development of an interdisciplinary Critical Care Fellowship program. NEUROANESTHESIA—We are seeking an academic faculty candidate trained in neurosurgical anesthesia to join a developing neuroanesthesia section. This opportunity requires a candidate with a primary interest in investigative research and teaching. A new spacious neuroscience facility at Duke fosters interdisciplinary relationships with neuropharmacology, neuroradiology, neurobiology, and neurology. The neuroscience program at Duke University is one of the five developing centers of excellence at this nationally prominent University. PEDIATRIC ANESTHESIOLOGIST/INTENSIVIST—Applicants for this position should have formal training beyond the 3-year continuum in the subspecialties of pediatric anesthesia and/or critical care or have recognized skills in lieu of normal fellowship training. VASCULAR THORACIC AND REGIONAL ANESTHESIA—Applicants for this position should have formal training beyond the 3-year continuum. We are seeking individuals with a primary interest in a teaching program, established clinical research interests, and experience in vascular thoracic anesthesia. Applicants for this position should be experienced in setting up a regional anesthesia block program for Residents in Training. Faculty candidates for all of the above positions must have a strong desire to conduct clinical research and teaching, in addition to clinical expertise. Academic titles and compensation for these positions will be commensurate with experience and credentials in education, clinical service, and research. Candidates must be board certified or equivalent and eligible for an unrestricted North Carolina medical license. Send letter of application and curriculum vitae to J. G. Reves, MD, Box 3094, Duke University Medical Center, Durham, NC 27710. Duke University is an EO/AA Employer.

845B/D

CALIFORNIA REDWOODS

Half-time position on Coast 4 hours north of San Francisco. Beautiful scenery, mild climate, great fishing, relaxed lifestyle, family-oriented community. Small hospital, agreeable medical staff. Ideal for the physician who wishes a steady income while enjoying blocks of free time to pursue other interests. For details, contact J. Russell, MD, P.O. Box 608, Fortuna, CA 95540, or call (707) 725-2833, (707) 725-3361.

847B/D

CALIFORNIA

Los Angeles County Harbor-UCLA Medical Center, Department of Anesthesiology. Opening in faculty position at the rank of assistant professor. Desire recent graduate of anesthesiology fellowship with research training. Board eligible or certified. Active clinical services, research, and independent residency program. Excellent South Bay area location. Ample academic career opportunities with joint UCLA and LA County appointments. Competitive compensations. Send CV and list of references to Chingmuh Lee, MD, Professor and Chairman, Department of Anesthesiology, Harbor-UCLA Medical Center, 1000 West Carson Street, Torrance, CA 90509. An Equal Opportunity Employer.

848BC

PAIN FELLOWSHIP

Available for 6 or 12 months beginning July 1, 1992, and January 1993. Primary emphasis on acute postoperative pain, regional anesthesia, and oncological pain. "State of the art" acute pain service. No OR or OB night calls. Please send CV to Sanford L. Klein, DDS, MD, Chairman, Department of Anesthesia, University of Medicine & Dentistry of New Jersey—Robert Wood Johnson Medical School, CN-19, New Brunswick, NJ 08903-0019. The UMDNJ is an Affirmative Action/Equal Employment Opportunity Employer, m/f/h/v, and a member of the University Health System of New Jersey.

849BC

ANESTHESIOLOGIST

Progressive, young, and expanding MD/CRNA group in suburban Kansas City, Missouri hospital is seeking BE/BC associate. Pain fellowship and/or interest in pain management desirable but not mandatory. Send CV to Don Adamson, P.O. Box 10370, Kansas City, MO 64111.

850BC

CALIFORNIA

An outstanding opportunity exists for you to join a successful Anesthesia Department. Located in a growing community hospital within easy reach of the San Francisco Bay area, the Pacific Coast, Yosemite, and Sequoia National Parks. The Hospital is offering an attractive compensation and benefits package including a competitive salary base, productivity incentives, and all insurances. Interview and relocation expenses are also being offered. Call Mike Stakebake, 1-800-327-1585, Ext. 107.

851BC

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Department of Anesthesia seeks candidates at the Assistant or Associate Professor level for teaching, research, and clinical responsibilities at the Veterans Administration Hospital in San Francisco. Duties include patient care, resident and student teaching, research or specialized clinical activity, and administrative responsibilities. Special areas of interest may include any aspect of anesthesia. Individuals with clinical and research expertise in pain management, neurosurgical anesthesia, or intensive care are actively sought. Ongoing peer-review funded research programs at this institution include (a) studies of perioperative myocardial ischemia, (b) basic coronary physiology studies, and (c) studies of the mechanism of anesthetic action and metabolism. Applicants interested in contributing to one of these active research groups are also sought. Board certification or board eligibility in anesthesiology is required. The University of California is an Equal Opportunity Affirmative Action Employer. Please forward curriculum vitae and three references to: Ronald D. Miller, MD, Professor and Chairman, Department of Anesthesia UCSF, 521 Parnassus Avenue, Box 0648, Room C-455, San Francisco, CA 94143-0648.

852BC

TENNESSEE

Expanding department requires additional anesthesiologists. Full-time positions available at levels of Instructor to Associate Professor with emphasis on teaching, patient care, and clinical research. Prerequisites: (1) Meet Tennessee license requirements. (2) ABA diplomat or eligible for ABA examination. All subspecialties needed. Excellent opportunity for anesthesiologists who want an ideal mix of private practice with teaching and clinical research. Send curriculum vitae, bibliography, and the names and addresses of three references to Roger S. Cicala, MD, Department of Anesthesiology, University of Tennessee, Memphis, 800 Madison Avenue, Memphis, TN 38163. The University of Tennessee is an Equal Opportunity Employer/Affirmative Action Register/Title IX/Section 504 Employer.

853B/D

PROFESSOR/ASSOCIATE PROFESSOR

Department of Anesthesiology, Loyola University Stritch School of Medicine invites applications for Chief of Anesthesia at VA Hines Affiliated Hospital. Administrative experience and academic excellence are a must. This position reports to the Chairman of the Department of Anesthesiology at Loyola University. Opportunities to do clinical and basic research. Desire to participate in teaching residents necessary. Excellent opportunity as a stepping stone to become a chairperson. Competitive salary and benefits with nonclinical time for academic/administrative growth. Send CV to Ms. Cindy Shipyor, Administrative Director, Loyola University Medical Center, 2160 South First Avenue, Maywood, IL 60153. Loyola University Medical Center is an Equal Opportunity Employer.

854BC

ASSOCIATE PROFESSOR/PROFESSOR

The Department of Anesthesiology at Loyola University Stritch School of Medicine, Maywood, Illinois, is recruiting an Associate Director, Pain Control Center, who should be a board-certified anesthesiologist. Prerequisites include experience in chronic and acute pain management and academic experience to warrant initial appointment as Associate Professor. Excellent clinical and basic research opportunities are available. Please reply with CV to Tadikonda L. K. Rao, MD, Professor and Chairman, Department of Anesthesiology, Loyola University Medical Center, 2160 South First Avenue, Maywood, IL 60153. Loyola University Medical Center is an Equal Opportunity Employer.

855BC

FELLOWSHIP—PEDIATRIC CARDIAC ANESTHESIA

Applications are being accepted for a 12-month academic fellowship (CA-4) starting in July 1991 and thereafter. Clinical training on dedicated service with 1000 cardiac OR and 400 Cath Lab cases per year. Research training for up to 6 months included. Address correspondence with CV to Paul R. Hickey, MD, Cardiac Anesthesia Service, Children's Hospital, 300 Longwood Avenue, Boston, MA 02115.

667EGIKAC

ANESTHESIOLOGISTS

Temple University School of Medicine has full-time faculty positions available for board-eligible anesthesiologists with training in a subspecialty area (cardiac anesthesia, critical care, and/or pain). Faculty rank will be commensurate with experience. Duties include patient care, teaching, and research. Send curriculum vitae to Christer Carlsson, MD, PhD, Chairman, Department of Anesthesiology, Temple University School of Medicine, Broad and Ontario

Streets, Philadelphia, PA 19140. An Equal Opportunity/Affirmative Action Employer.
856CD

Anesthesiologists needed at instructor and assistant professor levels. Must be board certified or board eligible. Duties include patient care, resident and medical student teaching, and research. Positions available at the University of Missouri-Columbia Health Sciences Center. Interested applicants send curriculum vitae to G.W.N. Eggers, Jr, MD, Professor and Chairman, Department of Anesthesiology, University of Missouri Health Sciences Center, Columbia, MO 65212. An Equal Opportunity/Affirmative Action Employer.
857C

ANESTHESIOLOGIST

Department of Anesthesiology at the SUNY Health Science Center in Syracuse, N.Y. is recruiting faculty at the instructor, assistant, and associate professor levels. Qualified individuals with a strong academic commitment in all types of anesthesia, critical care, and pain management are sought. SUNY Health Science Center is a tertiary-care center and provides clinical services also to the Syracuse Veterans Administration Hospital. Rank and salary are commensurate with experience. Must be board certified or board eligible and possess a New York State medical license. Please send letter, curriculum vitae, and names, addresses, and phone numbers of three references to Enrico M. Camporesi, MD, Professor and Chairman, Department of Anesthesiology, SUNY Health Science Center, Syracuse, NY 13210. The State University of New York Health Science Center is an Equal Opportunity/AA Employer.
858C/E

ARIZONA

Immediate opening for a BC/BE anesthesiologist to work 2 weeks each month in a well-equipped community hospital. The hospital is located in a beautiful resort and retirement area not far from the city. The position involves alternating with the present anesthesiologist in supervising CRNAs for routine cases with no pain, OB, cardiovascular, or neurosurgery. The compensation could be either salaried or based on a percentage and should be about 100–130K. Send resume and letter in confidence to P.O. Box 245, Sedona, AZ 86336.
859C

IOWA, SIOUX CITY—ANESTHESIOLOGISTS

Multiservice trauma hospital anesthesia practice expanding, two full-time positions available. University affiliated. Practice includes CRNA supervision and doing some cases. Minimal pediatrics and obstetrics. Active trauma, CV, and neuro practice. Board eligibility/certification desirable. Competitive remuneration including professional liability and disability insurances. A growing Premier Anesthesia practice. Send CV to Jerry H. Titel, MD, Chairman, Department of Anesthesia, 801 5th Street, Sioux City, IA 51101.
860C

UCSF PEDIATRIC ANESTHESIOLOGY FELLOWSHIP

The Departments of Anesthesiology at the University of California, San Francisco and Children's Hospital of Northern California, Oakland, California, are jointly offering two 1-year clinical fellowship positions (CA-4) in pediatric anesthesiology beginning in July 1992. The fellowship will include extensive operating room experience in all pediatric subspecialties in both institutions and critical care medicine exposure for neonates, older infants, and children. The fellows will spend 6 months in each institution. Send inquiries to Mark Rosen, MD, Director, Anesthesia Training Programs, c/o Dolores Scholz, Department of Anesthesia, S-455, University of California, San Francisco, San Francisco, CA 94143-0464.
861CD

Full-time anesthesiologists needed to join expanding M.D.A. group at 219-bed Healthsouth Medical Center in Birmingham, Alabama. Approximately 70% of surgery is orthopedic by world-renown surgeons. No hearts and no obstetrics. We have active and rapidly expanding pain service. Anesthesiologist needed to participate in pain service and/or supervise CRNAs in OR. Many attractive residential areas and good schools within short drive of hospital. Rapid partnership opportunity. Please respond to Anesthesia Services of Birmingham, P.C., P.O. Box 530590, Birmingham, AL 35253-0590, Attn: Administrator.
862C

CARDIAC ANESTHESIOLOGY FELLOWSHIP

CA-3 and CA-4 fellowship positions available starting July 1992. Full spectrum adult cardiac surgery. Opportunity for extensive training in invasive monitoring and transesophageal echocardiography. Research opportunities in cardiac pharmacology, physiology, and TEE. Please contact Z. Hillel, MD, PhD, Director, Cardiac Anesthesia, St. Luke's/Roosevelt Hospital, Amsterdam Avenue at 114th Street, New York, NY 10025.
863C/E

RESIDENCY IN ANESTHESIOLOGY

The Department of Anesthesiology and Critical Care Medicine at the University of New Mexico School of Medicine is expanding its residency program. Qualified applicants for the CA-1 to CA-3 levels starting July 1992 are invited to write to Director of Education, Department of Anesthesiology, UNM School of Medicine, Albuquerque, NM 87131-5216. The University of New Mexico is an Equal Opportunity Employer.
864C/F

UCLA—DEPARTMENT OF ANESTHESIOLOGY

LIVER TRANSPLANT FELLOWSHIP—Department of Anesthesiology, UCLA School of Medicine, active transplant service (200 transplants/year). Clinical and/or bench research depending on applicant's qualifications. Address inquiries to Marie Csete Prager, MD, UCLA Department of Anesthesiology, 10833 Le Conte Avenue, Los Angeles, CA 90024-1778. Equal Employment Opportunity (M/F) Employer.
865C/E

ACTIVE PAIN MANAGEMENT CLINIC PRACTICE

Anesthesiologist director. Located Central California Coast. Fully equipped including cryoanalgesia, cardioscope, pulse oximeter, defibrillator, and office business machines. Three hospitals in area. Will introduce. Call (408) 625-2386.
866CD

ANESTHESIOLOGIST/FLORIDA

Excellent starting opportunity, immediate opening. Growing 100-bed hospital in suburban community, 30 minutes north of Tampa Bay. Good salary, benefits, partnership in 2 years. P.O. Box 1166, Dade City, FL 33525. (813) 788-0411, Ext. 2315 or (813) 782-0285.
867C

CALIFORNIA

Anesthesiologist needed for Palm Springs group practice. Resort community. All types of anesthesia except hearts and trauma. Excellent compensation package leading to partnership. Please send CV to Director of Anesthesiology, 73-925 Highway 111, #L, Palm Desert, CA 92260.
868C

ANESTHESIA: UNIVERSITY OF IOWA FACULTY POSITIONS AT ALL RANKS

Excellent research facilities. Senior advice/consultation readily available. Must be board certified or in the examination process, eligible for Iowa medical licensure. University of Iowa and VAMC dual appointment possible. Submit curriculum vitae to John H. Tinker, MD, Professor and Head, Department of Anesthesia, University of Iowa College of Medicine, Iowa City, IA 52242. The University of Iowa and Veterans Administration Medical Center are

Equal Opportunity/Affirmative Action Employers.

869C

FELLOWSHIP—OBSTETRIC ANESTHESIA
Applications are being accepted for a 12-month academic fellowship (CA-4), starting on or about July 1992. Clinical training on dedicated service with 5000 obstetric deliveries, many in the "high risk" category. Clinical and animal research training included. Equal Opportunity Employer. Send CV to M. Finster, MD, Department of Anesthesiology, Columbia-Presbyterian Medical Center, 622 West 168th Street, New York, NY 10032.

870CD

MARYLAND
A well-respected, 4-MDA, 9-CRNA group seeks an experienced anesthesiologist to join them in practice. Affiliate with a progressive 200-bed regional referral center known for its comprehensive medical services, with the exception of open heart surgery. With a 35% increase in caseload over the last 2 years and continued increases expected, an incoming physician can expect rapid start-up time with a diversified caseload. Salary, benefits, and bonuses divided equally from day one. Partnership and pension after 12 months. Located in scenic Allegany mountains of western Maryland with easy access to the tremendous amenities offered by the Baltimore, Washington, and Pittsburgh areas. A sportsman's paradise, this area offers skiing, white water rafting, numerous state parks and large lakes, a nearby state university, superb housing values, and calming lifestyle. Contact Janice Schultz or Mary Wynkoop, Tyler and Company, 9040 Roswell Road, Suite 550, Atlanta, GA 30350. FAX CV to (404) 641-6414, or call (800) 333-3910 or (404) 641-6410.

871CD

The Department of Anesthesiology at the University of Texas Medical School in Houston is recruiting faculty at assistant professor, associate professor, and professor levels. Applicants must be board certified or board eligible and able to obtain a Texas medical license. The faculty positions include responsibilities for teaching, supervising and providing patient care, and participation in clinical or laboratory research and administrative functions of the department. The department has significant and expanding responsibilities in the areas of pain management, obstetrical anesthesia, neuroanesthesia, cardiac and vascular anesthesia, and hyperbaric medicine. Interested individuals should send a copy of curriculum vitae and names, addresses, phone numbers, and permission to contact three reference sources. Information should be sent to Alan S. Tonnesen, MD, Acting Chairman, Department of Anesthesiology, University of Texas Medical School, 6431 Fannin, Houston, TX 77030. The University of Texas is an equal opportunity employer. Women and minorities are encouraged to apply.

873C/H

WASHINGTON, D.C.
Positions available immediately and during the next year for full-time BE/BC anesthesiologists to join a growing MD/CRNA practice. Large ambulatory and challenging tertiary care caseload including all specialties except Pediatrics at University-affiliated hospital. Reasonable call schedule with competitive compensation package and partnership after one year. Send or fax CV to Barney S.H. Feinstein, MD, Chairman, Department of Anesthesia, Washington Hospital Center, 110 Irving Street, NW, Washington, DC 20010; Fax number (202) 877-5564 or call collect (202) 877-7500.

872CEGIK

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Prepare early for the ITE/written boards. Unique study program with practice questions and answers with explanations, guessing techniques, Keywords 1991, and much more. Call the original MEDTEXT: 1-800-695-6301; 24 hours. MC/V accepted.

757I/G

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The unique feature of these programs is the maximum class size of four students. Preparation for the written and oral exams are given separately in 3-day blocks in San Francisco and New York. FOR THE WRITTENS, techniques are taught for dealing with the multiple-choice questions. The basic sciences are stressed. FOR THE ORALS, the guided case discussions are stressed. Home study programs are provided. CALL (415) 321-1117.

763I/C

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For anesthesiologists and CRNAs. We can provide you with quality locum tenens services to meet your specific coverage needs. Or work locum tenens with us for a change in both your practice and your lifestyle. ReplaceMed * 1-800/736-8236 * PO Box 640 * Michigan City, IN 46360.

832A/L

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Providing top-quality CRNAs to meet your specific needs. Our CRNAs are screened to assure quality in performance as well as personal stability. License verification, curriculum vitae, references procured by us, AANA recertification, malpractice verification are supplied to you. Call 1-800-426-2349 any time.

755I/H

A WEEKEND OF MOCK ORAL EXAMS
Mock orals, not lectures. We are the original course in this format. 20 hours category I CME credit, two board-certified instructors, 12 students maximum. Dallas, March 6–8. ANESTHESIA EXAM REVIEW, 7128 Regents Park, Toledo, OH 43617. (419) 843-4480 or (813) 394-8780.

783C